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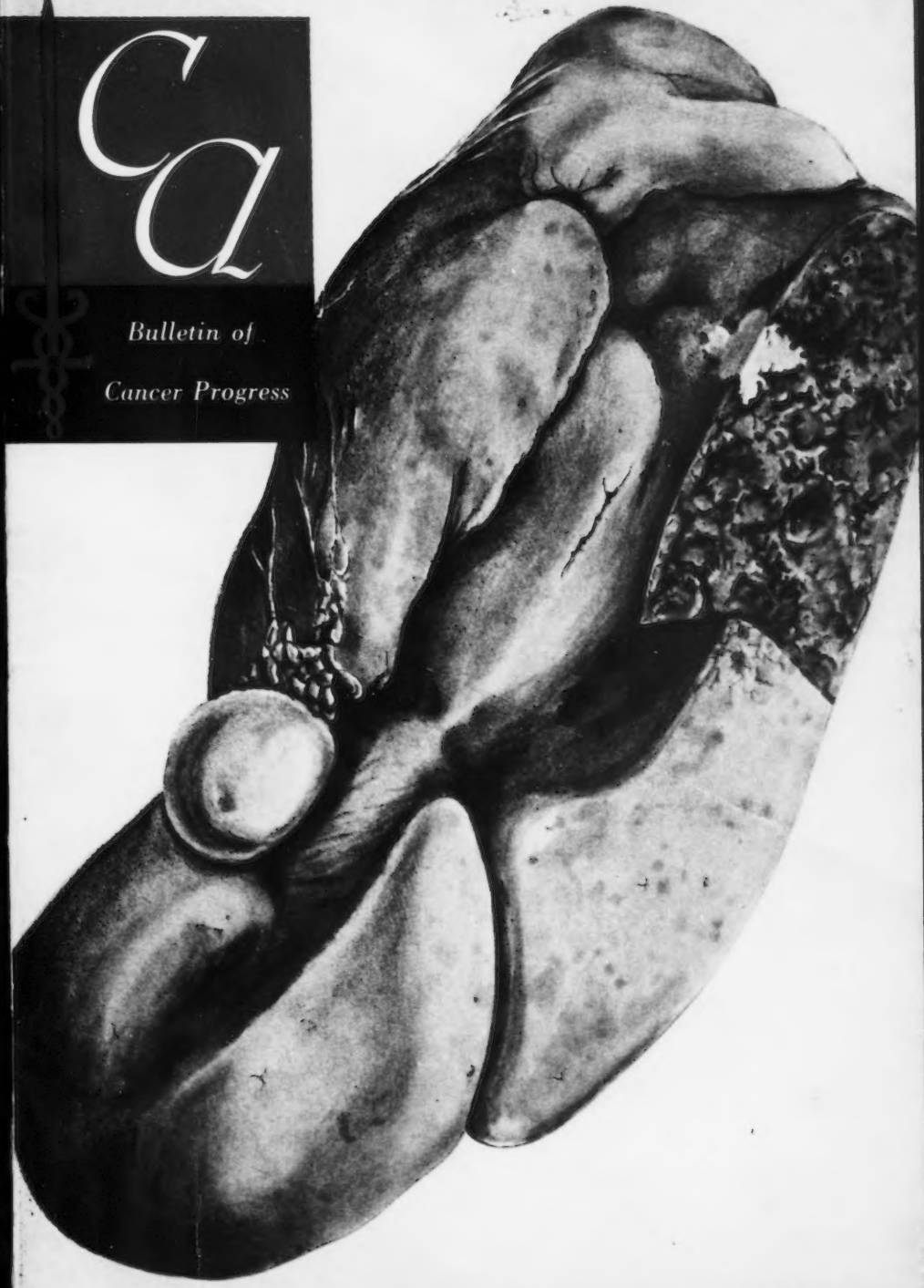
Cancer Progress



T. H. Chambers del. Ford & George, Lithographers, 54 Hatton Garden

breakthrough just around the corner?

Little did Hodgkin, Bennett and Virchow suppose that their new diseases of the lymphatic system, spleen and blood would one day be classified as malignant and neoplastic, or that their pioneer observations would lead to productive research into the causes and treatment of cancer a century later.

Much of current knowledge of the chemotherapy of cancer has resulted from studies of these lymphomatous diseases in man and animals. Leukemia is peculiarly adapted to the search for anticancer drugs, the efficacy of which may be estimated by simple hematological study of easily available, frequent samples.

It is reasonable to suppose that the long hoped-for solution of the cancer problem will result from research into the causes, nature, course and therapy of leukemia and lymphoma, and, judging by the little progress made in the control of these diseases in more than a century, that much more effort, time and money will be needed and that many more lives will be lost before it can be truly said "the breakthrough is just around the corner."

Cover—"Spleen (of Case IV.) W. G., cabinetmaker, aged 42, had usually resided near Carnaby market, a close-built, but not malarious, part of London . . . Has occasionally had bleeding from the gums and nose . . . gums were spongy, and his skin harsh, and he had a very well-defined tumour in the region of the spleen. On being questioned on this head, he stated it to be of very recent growth, and did not appear to have paid much attention to it. His sputa were occasionally tinged with blood, but I could not discover any stethoscopic signs of pulmonary disease. The tumour grew rapidly . . . I examined his blood under the microscope, and found in it a considerable number of large spherical corpuscles, about three or four times the size of the ordinary red globules. On the 1st of March he was attacked by violent epistaxis, which was stopped indeed after some difficulty by plugging the nose, but which weakened him so much that he died on the 9th.

"*Sectio Cadaveris.*—The blood was all fluid. The other viscera were healthy, except the spleen which was greatly enlarged. Its long circumference measured 27½ inches, its broadest circumference 18 inches. Its appearance outside was yellow, mottled, and smooth, and attached to it were some small supplementary spleens, also diseased, one of a singular round form. Its consistence was about that of a raw potato. The section presented a number of spots, as of ecchymosis from the rupture of small vessels. Near the surface, on the posterior part, was a lump of whitish deposit, like those sometimes found in the spleen, in cases of diseased heart."

Chambers, T. K.: Leucocythemia detected during life and after death; hypertrophy of the spleen. In Bennett, J. H.: Leucocythemia, or White Cell Blood in Relation to the Physiology of the Lymphatic Glandular System. Edinburgh. Sutherland and Knox. 1852: p. 24 and Plate II. [*See page 48.*]

NEWSLETTER

MARCH-APRIL, 1959

For seven successive years the Arizona Division of the American Cancer Society has staged a seminar for physicians and nurses. The sessions have become increasingly popular, not only because they afford escape to the warm January sun of Phoenix and Tucson (the meetings are held in each city on alternate years) but also because of the high caliber of speakers imported for the occasion. This year almost 400 physicians and more than 100 nurses from 20-odd states attended.

Among the newsier developments reported by speakers were these:

Hunt (U. of Neb. College of Medicine) cited a recent survey which showed that, in Nebraska, the death rate from cervical cancer has fallen from 11.5 per 100,000 in 1946-48 to 6.8 during 1954-57. This remarkable reduction in fatalities was part of the trend of the last 30 years, during which the percentage of survivors increased about three-fold. Hunt attributed this added salvage to: (1) earlier diagnosis -- both patients and doctors are more alert to early symptoms, and vaginal smears have made possible early diagnosis and prompt treatment; (2) prevention -- surgical or radiological destruction of precancerous lesions; and (3) better treatment -- constantly improved methods in both surgery and radiotherapy.

Virus as a cause of cancer "is no longer a theory -- it is a fact," Bostick (U. of Calif.) asserted. He cited as evidence the findings by a mounting number of scientists that cancers can be induced by tumor filtrates. And he described his own work, in which he induces a rapidly lethal encephalitis by injecting mice with particle-containing filtrates from human Hodgkin's disease tissues. He expressed the opinion that polio-type vaccination would be effective against many kinds of cancer. As for humans, the knotty problem of whom to vaccinate and against which agent still lacks an answer. He also countenanced the possibility that a blood test may be developed to indicate the presence of cancer viruses. "The basic question which now remains," he said, "is whether or not all cancers are the result of virus-

type infections; maybe these viruses are so intimately connected with a cell's function that they are very difficult to distinguish from some normal cellular components, such as plasmagenes."

Overholt (Tufts) sternly lectured the physicians on their cigarette "addiction." Pointing to statistics that indicate that a person can reduce by nine-fold his chances of developing lung cancer by avoiding cigarettes, he stated: "Our profession should join public health agencies, the clergy, teachers and parents in disseminating knowledge about tobacco and health. Efforts should be focused upon young people who either have not started to smoke or who have not become addicted to the drug. Doctors themselves can be of most help by setting a good example. If they smoke, they should attempt to cure their own addiction. They will not only be an example for their friends and patients, but they will reduce significantly the risk of their own premature death by lung cancer. Doctors have an opportunity to save more lives through efforts in preventing illness than in rescuing some after they fall prey to serious disease."

Brunschwig (Cornell) reported that of 300 pelvic exenterations performed on patients up to 1953, a total of 53 patients became five-year survivors -- the patients were clinically free of cancer, he said. Some of the early patients who underwent this radical procedure are alive and well 10 and 11 years following operation. The operation, which involves removal of virtually all pelvic organs, is of particular value to patients with recurrence following irradiation -- re-irradiation does little good as a rule, he said. In his series, about 38 per cent of "radiation failure" cases who could be treated conservatively (hysterectomy and lymph node dissection only) survived five or more years -- a little more than twice the salvage of cases in which exenteration was indicated.

Radiologist Hodes (U. of Pa.), Neurosurgeon Boldrey (U. of Calif.) and Pathologist Kernohan (Mayo) agreed that the number of brain tumors diagnosed each year is rising. This they attributed to better diagnostic methods -- patients with brain tumors less often are being diagnosed as convulsives, mental cases and stroke victims. Thanks to hypothermia and induced hypotension for control of bleeding and numerous other surgical advances, they said, operative mortality for brain tumors is no higher than it is in

(Continued after page 72)

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TOPIC: LEUKEMIA

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at a glance . . .

one-minute abstracts of the literature on leukemia

Chemotherapy of Acute Leukemia

Sixty-five patients with acute leukemia were allocated at random to two combination chemotherapeutic regimens. All patients were given 6-mercaptopurine 3 mg. per Kg. daily. One group was given in addition 2.5 mg. methotrexate daily and the other group 7.5 mg. methotrexate every three days. No differences in frequency of remission, extent of remission or toxicity were observed between the two groups. Remissions occurred only in children with acute lymphocytic leukemia and in adults with acute myelocytic leukemia. Remissions in adults were longer than those in children. Remission, partial or complete, occurred in 36 per cent of the children and in 19 per cent of the adults. There were 17 deaths, eight in the first 10 days presumably from leukemia and not drug toxicity. Five patients died with hypoplastic marrows ascribed to drug toxicity. The mean survival time from onset of symptoms for all the children was 12 months; for adults, seven months. This figure is similar to that reported from other clinics, showing that the patients were not harmed by these studies.

Frei, E., III; Holland, J. F.; Schneiderman, M. A.; Pinkel, D.; Selkirk, G.; Freireich, E. J.; Silver, R. T.; Gold, G. L., and Regelson, W.: A comparative study of two regimens of combination chemotherapy in acute leukemia. Blood 13:1126-1148, Dec., 1958.

Leukemia not Neoplastic

From comparative studies of the action of antigens from the cell membrane-cytoplasm complex of the entire leukocyte upon various leukocyte types, the authors conclude that leukemia is not a neoplastic process. These antigens produce agglutinating antibodies specific for lymphocyte, granulocyte, monocyte and plasma cell as well as for their embryonal stages from blast to mature form. Normal and leukemic lymphocytes are antigenically similar but are dissimilar from the neoplastic lymphocyte, indicating that the chemical compositions of normal and leukemic lymphocytes are alike but different from that of malignant lymphocytes. This suggests basically different etiologies for leukemia and neoplasia. Hodgkin's disease has no antigenic similarity to either leukemia or neoplasia. Cells of thymoma, lymphosarcoma, plasma cell myeloma and monocytic leukemia have similar antigenic properties. This indicates that monocytic leukemia may be allied to neoplasia rather than to leukemia. On the basis of leukoagglutination these studies suggest that leukemia, other than the monocytic type, is not a neoplastic process.

Steinberg, B., and Martin, R. A.: Leukoagglutination; relation of leukemia to cancer. Acta haemat. 19:241-252, Apr.-May, 1958.

Mongolism and Leukemia

Mongolism and leukemia occur simultaneously far more frequently than would be expected by chance calculated from the incidences of the two conditions. This suggests a common biologic factor and possible etiologic relationship. The etiologic process in mongolism exerts its influence in the sixth to ninth week of the fetal period. If, at this time, a common prenatal factor was biologically concerned, it might be possible to demonstrate in leukemic patients an increased frequency of some of the generally recognized stigmata of mongolism even in the absence of the frank, typical syndrome. Accordingly 59 children with acute leukemia were examined for brachycephaly, dermatoglyphic patterns, hypoplasia of the middle phalanx of the fifth finger, and congenital cardiac anomalies. Two of the 59 leukemics had associated mongolism. The other 57 were studied by the usual anthropometric body measurements. Thirty of the children had satisfactory roentgenograms of the bones of the wrist and hand. This investigation failed to demonstrate increased frequency of these stigmata of mongolism in children with acute leukemia. Stigmata common to both conditions may not have been included and it is possible that the various stigmata may be in so subtle form as to escape the techniques used here. In this group of 59 children, the two with associated mongolism and 15 others were two years of age or younger at the time of initial examination. Clinical documentation of acute leukemia needs to include a broader spectrum of physical and physiologic data.

Sutow, W. W.: Incidence of stigmata of mongolism in children with acute leukemia. Pediatrics 21:958-962, June, 1958.

Leukemia Records

From a survey of the data on leukemia contained in the records of the Ministry of Pensions and National Insurance (British), the authors were impressed by certain fundamental uncertainties concerning the true incidence of leukemia in the general population, the apparent increase in death rate from leukemia in the general population in the period 1911 to 1955, and the identification of the various types of leukemia. Some cases of leukemia in infancy are confused with acute infections. Some cases in adults past middle age have been recorded as cerebral hemorrhage. It is improbable that a death will be certified as due to leukemia unless hematological investigation has been made. The incidence of leukemia is, therefore, more likely to be under- than over-estimated. Recent publicity concerning the leukemogenic effects of irradiation in ankylosing spondylitis, goiter, persistent thymus, etc., has made the physician leukemia conscious, and it may be expected that recorded rates of incidence in the near future will not be so far below the actual figures. Between 1911 and 1955 the incidence rate for males increased 4.4 times; for females, 4.3. This suggests that the factors responsible for the increase apply to both sexes. The diagnosis of cell type in leukemia, particularly as recorded on death certificates, is too unreliable for any conclusions to be drawn from it. Although some of the apparent increase in death rate from leukemia is due to improvement in diagnostic facilities, the greater part of it appears to be real.

Lea, A. J., and Abbatt, J. D.: Leukaemia; doubts and difficulties. Lancet 2:231-233, Aug. 2, 1958.

Chemotherapy of Myeloid Leukemia

A review of 3926 cases of myeloid leukemia reveals great difficulty in evaluation of the many methods of chemical therapy employed since 1949. Many of the reports in the literature do not give the number of patients responding to therapy and some fail to report even the number of cases treated. Lack of objective standards for satisfactory results adds to the difficulty of evaluation. Some reports are supported by detailed laboratory and clinical findings; others describe only subjective reactions and general impressions of the therapy. Myleran is the choice of many investigators. There are but few reports of its toxicity, although several patients were

reported to have had hastened downhill courses with bone marrow failure following its use. Nitrogen mustard shows the highest remission rate but its toxic effects are referred to in many reports. Radiophosphorus is sometimes contraindicated as it may transform chronic into acute myeloid leukemia. Urethane is generally considered to be too toxic for use in this form of leukemia. The courses of both acute and chronic myelocytic leukemias have been hastened by the use of cortisone, ACTH and the folic acid antagonists. Some investigators consider the folic acid antagonists and triethylene melamine contraindicated in acute leukemia. Good hematological remissions, but also severe toxicity, are reported following use of the folic acid antagonists. 6-Mercaptopurine is effective in both acute and chronic myeloid leukemias and is less toxic than some of the other drugs. Other chemicals used are: arsenic, radiogold, colchicines, phosphoramides and antibiotics.

Sampey, J. R.: Limitations in the chemical treatment of myeloid leukemia; a study of 3926 cases. J. South Carolina M. A. 54:242-244, July, 1958.

Leukemia and Virus

Leukemia can be induced in mice not only by inoculation of filtrates containing a transmissible oncogenic agent (virus?) but also by application of carcinogenic chemicals, injection of estrogens and by total body x-ray irradiation. The author assumes theoretically that these carcinogenic chemicals, estrogens and ionizing radiation may induce leukemia indirectly by activating latent viruses carried in an inactive form in apparently healthy hosts. A group of healthy, young C3H mice received 159 to 200 r, 4 to 5 times, at weekly intervals. Fifty per cent of the mice developed leukemia. From these leukemic donors, filtered extracts were prepared and inoculated into 148 newborn mice of the same strain. Sixteen (11 per cent) of these developed leukemia in an average of 13 months, and 7 (5 per cent) developed parotid gland tumors in an average of 10 months. In the author's experience with thousands of untreated C3H mice he has seen only one spontaneous parotid tumor and less than 0.5 per cent of spontaneous leukemia. In a control series, extracts from healthy C3H donors were inoculated into 186 newborn mice of the same strain. Only one (0.5 per cent) developed leukemia at 17 months, and 14 (7.5 per cent) developed parotid tumors at 4½ months. These results suggest that a latent leukemic agent, carried in mice of a low leukemic strain, can be triggered into activity by ionizing radiation, and transmitted by inoculation into newborn mice of the same strain.

Gross, L.: Attempt to recover filterable agent from x-ray-induced leukemia. Acta haemat. 19:353-361, June, 1958.

Leukemia from Radiation

Death of a 10-month-old infant from acute granulocytic leukemia is reported. The mother had been radiographed for fetal presentation three times during the two weeks before delivery, the last time on the day before delivery. There were five exposures, three anteroposterior and two lateral. The mother was very obese, 238 pounds, and the exposure factors were much greater than usual. The authors, from an analysis of the five films, reconstituted the probable dosages delivered to the center of the fetus, and outlined technical procedures whereby the estimated dosage could have been reduced by 92 per cent. These precautionary measures include: additional tube filtration of 2 mm. of aluminum, use of high-speed screens, doubling the development time of the film, increasing the anode film distance in erect lateral films of the pelvis from 40 to 80 inches and use of high kilovoltage techniques. These changes, even in this obese woman, would have reduced the dose to the center of the fetus from one known to be leukemogenic in adults to approximately 1.9 r, only 8 per cent of that actually received, and it would be still lower in the average obstetrical case.

Gunz, F. W.; Borthwick, R. A., and Rolleston, G. L.: Acute leukaemia in an infant following excessive intrauterine irradiation. Lancet 2:190-192, July 26, 1958.

Leukemia in Childhood

Leukemia is an inevitably fatal condition which is increasing in incidence. Each year there are 11,000 new cases in the United States. The leukemias are classified as acute or chronic and according to their similarities to the major normal leukocytic components of the blood—granulocytic, lymphocytic and monocytic. In young children leukemia is acute lymphocytic in 80 per cent of cases. It is believed that some external force may trigger an intrinsic etiologic mechanism. The incidence of leukemia is distinctly higher in mongolism than in the general population. Radiation is accepted as an etiologic factor in radiologists, populations exposed to atomic bombs and children treated for thymic enlargement. Newer knowledge of blood transfusions and the introduction of antibiotics have added to the life span of leukemic patients. And within the last few years several new drugs have contributed to increase the length of survival. Among these are the antimetabolites and the steroids. In 1948, aminopterin, an analogue of folic acid was used with success. This was followed by amethopterin (methotrexate). Carefully controlled doses of these drugs give a relatively mild folic acid deficiency—sufficient to damage the leukemic cells but insufficient to damage normal cells. The most commonly used antipurine drug is 6-mercaptopurine. Both it and methotrexate are generally administered orally in 2.5 mg. daily doses. Of the group ACTH, cortisone, hydrocortisone, prednisone and prednisolone, the last two are least toxic and, therefore, most generally used. With these new drugs the life span has been increased from four and a half months in 1948 to more than two years.

Leikin, S.: Therapy of childhood leukemia. M. Ann. District of Columbia 28:11-14, Jan., 1959.

Anemia in Leukemia

The anemia in leukemia is not invariably due to a simple failure of erythropoiesis. Several studies have shown the anemia to be due to increased destruction rather than to decreased production of red cells, and occult hemolysis is not uncommon. The authors used a combined radioactive iron and radioactive chromium technique for simultaneous measurements of erythrocyte production and destruction in treated and untreated patients with leukemia. Seventeen patients were studied before treatment and seven before and after treatment. Great variability was shown in the relative roles of erythropoietic failure and short erythrocyte life. In six patients with anemia erythrocyte survival was normal and the anemia was due solely to failure of erythrocyte production. In nine of the anemic patients hemolysis was demonstrable. There was no correlation of the type of leukemia with the mechanism of the anemia. The technique employed proved valid for assessing the effect of various forms of treatment on erythrocyte production and destruction, a knowledge of which is essential in maintaining adequate hemoglobin levels in the leukemic patient.

Wetherley-Mein, G.; Epstein, I. S.; Foster, W. D., and Grimes, A. J.: Mechanisms of anemia in leukaemia. Brit. J. Haemat. 4:281-291, July, 1958.

Leukocyte Antibodies in Leukemias and Lymphomas

A comparatively simple technique for detecting antileukocyte antibodies in the blood serum of patients with various pathologic states is described. Patients with Hodgkin's disease with depressed leukocyte count, and not previously given drug therapy that could cause the leukopenia, showed sharply different results of leukotoxin tests from those of patients with Hodgkin's disease having normal leukocyte counts. None of the patients with normal counts had a positive test, and all of the leukopenic patients had positive tests. Search for leukocyte and platelet antibodies was of significant aid in clinical management of Hodgkin's disease. Patients with evidence of autoantibody generally required steroid therapy at some time during the course of their disease and were often temporarily improved by splenectomy, which made possible the

more energetic and more extended use of chemotherapy. Strongly positive antibody tests were also obtained from the leukopenic serums of patients with acute aleukemic leukemia. Three of the four cases of positive agglutinins in the aleukemic group represented cases of acute histiocytic leukemia, and two of these three showed markedly abnormal globulins on electrophoretic analysis. Chemical and electrophoretic studies show the activity of antileukocyte antibody to have at least two components: one with characteristics of alpha globulin and one with those of beta globulin.

Tullis, J. L.: Prevalence, nature and identification of leukocyte antibodies. New England J. Med. 258:569-578, March 20, 1958.

Incidence of Leukemia

Age-specific mortality rates from leukemia for each race and sex were computed for each year from 1921 to 1955, for the registration states. The upward trend of mortality from leukemia is decreasing. This steady decrease in the rate of increase of mortality from leukemia in every age group of the white population under 75 years of age is inconsistent with the theory that leukemogenic factors in the American environment have increased sharply in the last 15 years. It suggests rather that exposure of the general population to whatever causes operate to induce leukemia has recently decreased. The rate of increase among white persons has declined since about 1940. For the entire population the per cent increase rate dropped from 64 between 1930 and 1940 to 43 between 1940 and 1950. Incidentally it was shown that between 1940 and 1950 there was a smaller increase in mortality from leukemia among physicians than among white males of the same ages in the general population.

Gilliam, A. G., and Walter, W. A.: Trends of mortality from leukemia in the United States, 1921-55. Pub. Health Rep. 73:773-784, Sept., 1958.

Leukemia in Pregnancy

This report is the first review of leukemia in pregnancy since 1943. It reflects considerable improvement in the management of these cases. The mean total survival time before 1943 was 10 weeks, and in the present cases reviewed 5.9 months; and fetal mortality declined from 60 to 38 per cent. There is convincing evidence that the placenta acts as a complete barrier to spread of leukemia from mother to fetus; but placental transmission of Hodgkin's disease has been reported in three of a series of 32 cases. The greatest fetal difficulty is prematurity—7.7 months was the average duration of gestation in the entire series reported. Of the three cases added by the present authors to the several series reviewed, one was chloroma, yielding at autopsy the characteristic color phenomena. Antifolic acid agents are absolutely contraindicated in the first trimester of pregnancy because of their abortifacient properties. The rapidly effective steroids, as meticortin, are best for all three trimesters. Aminopterin, amethopterin and 6-mercaptopurine should be reserved for use in the second and third trimesters when steroid control fails. Fetal adrenal atrophy must be looked for and treated in those cases of long-continued, intensive adrenal steroid therapy during pregnancy. Fibrinogenopenia — antepartum, intrapartum and postpartum—corrected by prompt restorative therapy may prove of value in the control of hemorrhagic diatheses.

Yahia, C.; Hyman, G. A., and Phillips, L. L.: Acute leukemia and pregnancy. Obst. & Gynec. Surv. 13:1-21, Feb., 1958.

Virus Etiology of Leukemia

Cell-free agents from human leukemia were injected into low leukemic strains of mice and the leukemogenic effects noted. Extracts from the spleen, lymph nodes, bone marrow, brain, tonsils and blood were studied. Control extracts were made from normal tissues and from other human tumors—lung cancer, sarcomas and polyposis. Centrifuged saline extracts of human leukemic tissue caused leukemia in 34 per cent of mice in an average period of 3.7 months. In the controls, leukemia occurred in 3 per cent in 4.7 months.

Human sarcoma extracts gave a higher incidence of leukemia. The active leukemogenic agent was shown to be lipoproteins. Attempts to determine the living or nonliving nature of the leukemia factor resulted in finding it similar in features to other ordinary viruses. The number of cases of leukemia that can be ascribed etiologically to ionizing radiation and certain chemical substances is negligible compared with the total incidence of leukemia. It is highly probable that these remaining, majority cases of leukemia are caused by a cell-free agent having viral properties, and existing in a latent form in many apparently healthy people. This leukemia agent is triggered into activity by exposure to radiation, hormone imbalance, etc. Studies of the chemical identifications of the active agent should be made.

Bergoltz, V. M.: Experimental studies of the [a]etiology of leukaemia in men; a review. Neoplasma 5:337-347, No. 4, 1958.

Gastrointestinal Lymphoma

At Duke University Hospital between 1930 and 1952, 18 patients with gastric lymphosarcoma, 11 with lymphoma of the small bowel, one with lesion in the cecum and one with lesion in the transverse colon were treated by operation, radiation and chemotherapy. Seven of the 18 patients with gastric lesions lived for five years or longer, four being alive now. Three of the 11 patients with small bowel involvement lived five years or longer, all three being alive now. The two patients with lesions in the cecum and in the transverse colon died two months and 10 days after operation respectively. Malignant lymphomas of the gastrointestinal tract remain well localized for long periods. The prognosis for gastric lymphosarcoma is favorable if the lesion has not spread beyond the regional lymph nodes, even when the tumor is quite large. Results from radiation therapy and from chemotherapy with nitrogen mustard and TEM did not compare with those from surgery. Wide excision with postoperative x-ray therapy is the best form of curative management. Classification of malignant lymphomas is based on microscopic appearance: (1) stem cell lymphoma, (2) clasmatocytic lymphoma, (3) lymphoblastic lymphoma, (4) lymphocytic lymphoma, (5) Hodgkin's lymphoma, (6) Hodgkin's sarcoma, and (7) follicular lymphoma.

Frazer, J. W., Jr.: Malignant lymphomas of the gastrointestinal tract. Surg., Gynec. & Obst. 108:182-190, Feb., 1959.

Myleran for Polycythemia Vera

Myleran produces full remission in patients with polycythemia vera given an average dose of 29.4 mg. a week in 2 mg. doses. Increased dosage is not necessary for subsequent remissions. In five patients with nine relapses, remissions—seven complete, two partial—have lasted from three to 20 months. Clinical manifestations and abnormal physical findings, including hypertension and splenogemaly, disappeared and the blood improved. Hemoglobin, red blood cell, and hematocrit levels were reduced and white blood cell levels and platelets decreased significantly when their levels were originally above normal. Possibly myleran may not only reduce erythropoiesis but also qualitatively alter red cell formation, so that erythrocyte longevity is decreased and the volume of red cells is further reduced. Myleran is a chemical of the sulfonic acid ester group, which produces leukopenia in human beings and has been successfully used in treating chronic granulocytic leukemia. Further trial of myleran seems warranted, since the drug has the following advantages: no need for radiation, low cost, easy administration, no treatment other than blood counts at weekly intervals, safety, and no side effects.

Wald, N.; Hoshino, T., and Sears, M. E.: Therapy of polycythemia vera with myleran. Blood 13:757-762, Aug., 1958.

6-Chloropurine in Leukemia

Thirty patients, from 15 to 72 years of age, with predominantly blastic type leukemias were treated with 6-chloropurine and the results compared with those from 6-mercaptopurine in another group. In the

former group of 30 patients complete remissions were obtained in three and partial remissions in eight. Four patients known to be resistant to 6-mercaptopurine also failed to respond to 6-chloropurine. Three of four patients with chronic granulocytic leukemia responded to 6-chloropurine. In lymphomas, 6-chloropurine gave slight objective improvement, but only at the point of hematologic toxicity. Jaundice was a frequent complication, but it could not be related definitely to therapy. The two drugs have similar mechanisms and ranges of therapeutic activity; but 6-chloropurine appears to be slightly superior in acute leukemia in adults.

Ellison, R. R.; Karnofsky, D. A., and Burchenal, J. H.: Clinical evaluation of 6-chloropurine in leukemia in adults. Blood 13:705-724, Aug., 1958.

Neurologic Complications of Lymphosarcoma

A patient with generalized lymphosarcoma with involvement of the central nervous system was presented in clinicopathologic conference at Roswell Park Memorial Institute. The patient was a white male 32 years of age. Surgical exploration at another hospital revealed intussusception resulting from a tumor in the wall of the small intestine. Primary resection and anastomosis were performed. Histologic diagnosis was lymphosarcoma. After operation palpable lymph nodes appeared in axilla and groin and were examined by biopsy. They were diagnosed as granuloma or lymphosarcoma. Following a four-month asymptomatic period, abdominal cramps, nausea and vomiting developed, probably from obstruction or intussusception from an intrinsic tumor. Dramatic clinical improvement followed administration of nitrogen mustard 0.4 mg. per Kg. over four days. Two months later he developed symptoms of gastric ulcer and was unsuccessfully treated medically. A month later he developed left facial palsy. A second course of nitrogen mustard therapy relieved the gastrointestinal symptoms but the facial palsy remained. One month later he developed progressive neurologic symptoms—headache, paralysis of left oculomotor nerve, deafness on the left side. and involvement of the left hypoglossal, both glossopharyngeal and right facial nerves. A third course of nitrogen mustard therapy gave transient improvement, but the neurologic symptoms progressed rapidly involving the left third, seventh, eighth and twelfth cranial nerves, the right sixth and seventh and the left upper cervical nerves. He died ten months after the initial onset of symptoms and three months after onset of the neurological symptoms.

Pickren, J. W., and Sokal, J.: Clinicopathologic conference. New York J. Med. 58: 3311-3314, Oct. 15, 1958.

Chemotherapy of Leukemia

Current chemotherapy, although unsuccessful as a cure for leukemia, gives increase in survival times in the acute cases and greater comfort to the acute and chronic patients. The different effects of the drugs employed in the various forms of leukemia make necessary a good differential diagnostic knowledge among the several types. In the treatment of acute leukemia, blood replacement, maintenance of fluid balance and antibiotic therapy often make survival possible until the specific drug becomes effective. Among the thousands of compounds tried in leukemic therapy only a few have been found effective. The folic acid antagonists may cause stomatitis, alopecia, pharyngitis, diarrhea, aplasia of the bone marrow and gastrointestinal hemorrhage. Frequent blood examinations are necessary to follow results of treatment. Oral dosage is preferred. The folic acid antagonists are more effective in acute lymphatic than in acute myelogenous leukemia. ACTH and cortisone, now largely superseded by prednisone and prednisolone, give better results in children than in adults. These drugs constitute the treatment of choice in acute lymphatic leukemia. Like the folic acid antagonists, 6-mercaptopurine has important toxic effects. It may cause leukopenia, anemia and thrombocytopenia. Frequent blood counts are necessary dur-

ing a course of treatment. Survival time in children is increased by 6-mercaptopurine, but not in adults. When resistance to one drug results another is used. In desperately ill patients massive doses of prednisolone are often effective. Time honored x-ray therapy is still an important method in chronic leukemia. Among the other agents used in treatment of the chronic forms of leukemia are P^{32}, nitrogen mustard, triethylene melamine and the phosphoramides—TEPA and ThioTEPA. The author is of the opinion that of these only P^{32} will survive as an important method of treatment. Myleran has been found to be effective in some cases refractory to irradiation. It is also more convenient and less expensive than x ray and P^{32}, and it lacks the undesirable side effects often accompanying deep x-ray therapy. Chlorambucil is most useful in some cases of chronic lymphatic leukemia but further work will determine its true place in therapy. Considerable difference of opinion exists as to whether the asymptomatic chronic leukemia patient should be treated. The author states that the future may well prove that regular treatments of all patients with drugs such as myleran will extend their periods of survival. Confirmation will require long-term study.

Green, R. A.: Chemotherapy of leukemia. Minnesota Med. 41:491-498, July, 1958.

Prednisone in Leukemia

Ten adult patients with acute leukemia were treated with 1000 mg. prednisone or prednisolone daily for two weeks and ten with 250 mg. daily. Three complete and one partial remission occurred in the former group and two complete and one partial remission in the latter group. In a third group of ten patients treated with 100 mg. daily there were only brief and partial remissions. Some of the remissions occurred in patients receiving 6-mercaptopurine in addition, so that not all remissions can be credited to prednisone and prednisolone. Toxic reactions to these steroids were in proportion to dosage. All patients could tolerate 250 mg. daily for two weeks. Results of this study show prednisone to be as effective as 6-mercaptopurine without so great toxic effects. In most patients remarkable symptomatic improvement was evident in the first 24 to 48 hours. It is apparent that corticosteroids profoundly affect the rapidly proliferating primitive cell of acute leukemia, but whether this action is antimitotic or antimetabolic is not known.

Granville, N. B.; Rubio, F., Jr.; Unugur, A.; Schulman, E., and Dameshek, W.: Treatment of acute leukemia in adults with massive doses of prednisone and prednisolone. New England J. Med. 259:207-213, July 31, 1958.

Treatment of Leukemia

Resistance to all forms of therapy of leukemia ultimately occurs. Therapy favorable in acute leukemia may be unfavorable in chronic leukemia. In the early stages of chronic lymphocytic leukemia, if there are no constitutional symptoms, treatment may be withheld. Roentgen-ray therapy is the treatment of choice for localized symptomatic leukemic infiltrates. Alkylating agents have antitumor effects by virtue of their alkyl radicals combining with the phosphate moiety of desoxyribonucleic acid, thus interfering with cell division. Myleran is the drug of choice in chronic myelogenous leukemia, and chlorambucil in chronic lymphocytic leukemia. Gross resistance to x rays and myleran does not occur so that when either fails to give remission the other may be employed to induce another remission. Remissions from any drug or x rays become gradually less complete and less frequent, so that finally resistance to all agents occurs. In this acute phase of chronic leukemia 6-mercaptopurine occasionally gives transient improvement. It is very uncertain that any form of treatment lengthens life in chronic leukemia. On the other hand, in acute leukemia considerable progress has been made in prolonging survival by the use of agents that interfere with metabolism—antimetabolites, of which the most widely used are the folic acid antagonists (aminopterin and amethopterin) and 6-mercaptopurine.

Frei, E., III: The treatment of leukemia. GP 18:98-100, Nov., 1958.

Keeping up

Bloodless Cancer Surgery

The physician-dentist author, twenty years ago reported successful dental extractions in hemophiliacs by the use of elastic ligatures. In the present communication he extends and adapts the technique to removal of malignant growths at accessible body sites. By various modifications of the technique, elastic constriction was applied to the tissues at the base of the tumors. Gradual tightening of the constricting apparatus produced progressive limitation of the vascular supply, resulting in a dry, shriveling mummification and eventual exfoliation. This bloodless and usually painless process minimized the extent of denuded base. There was no need for surface covering of the remaining defect, if any. Complete exfoliation of three skin cancers was accomplished by this technique in 8, 10 and 14 days without recurrence or scarring. The author ascribes the success of this procedure partly to antigen formation resulting from the slow destruction of the tumor process. The method has sufficient advantages over conventional surgical procedure to warrant further investigation.

Dalitsch, W. W.: Induced regression of neoplasms by the controlled limitation of vascular supply; a method for the removal of some tumor growths with implications of certain beneficial effects. Am. J. Surg. 96:771-775, Dec., 1958.

Multiple Primary Cancer

A second carcinoma must be suspected in all patients with a known carcinoma of the large bowel. Familial polyposis and chronic ulcerative colitis are known to predispose to multiple primary carcinoma of the colon and rectum. Members of polyposis families must be followed carefully. Every member having the disease should be urged to undergo early total colectomy before malignant degeneration occurs. The incidence of cancer increases with the duration of chronic ulcerative colitis—as high as 30 per cent after ten years. Adenomas, or polyps, are generally considered to be precancerous and complete excision is the treatment of choice. The surgeon must always consider the possibility of more than one lesion and make every effort to remove them. Introduction of a sterile proctoscope into the remaining colon prior to anastomosis is recommended. After operation for cancer of the large bowel, the patient should be followed carefully with regular proctoscopic examinations to ensure finding either a recurrence or a new primary lesion.

Passmore, R. C., and Smith, G. A.: Multiple primary malignant lesions of the large bowel. Missouri Med. 55:1305-1307, Dec., 1958.

Resistance to Cancer

Some cancers have rapid evolution and progress without evidence of a delaying response by the body tissues while others progress slowly taking a number of years for full extension. A third group is rendered incapable of spread or even made to disappear by the resistant body tissues. The most radical and apparently complete resection may be followed by widespread, rapidly progressive metastases and a palliative resection undertaken with no hope

with Cancer

of cure may result in an extraordinarily long period of well being for the patient. And long periods, up to 30 years, may elapse before an excision of a human malignant tumor and the appearance of a recurrence. Examination of various organs at autopsy reveals many latent carcinomas —prostate, lung, kidney and thyroid. The rare self-healing epitheliomas are illustrations of the effectiveness of host resistance. Variation in growth rate of tumors is much more likely to arise from alterations in the patient's resistance than to fluctuations in virulence of the tumor. There is undoubtedly a resistance to cancer in some individuals and an increased susceptibility in others. This balance of power between neoplastic and reactive influences has been termed "biologic predeterminism." Until recently it was thought that, since a cancer cell is of the body's own pattern, no effective differential immunological attack against it was possible; but in view of recent research, animal and human, it is conceivable that there is sufficient antigenic difference to be effective. It is possible that the body can develop some degree of immunity, either local or general, and it might be possible to influence either the cancer cells or their environment so that the balance in favor of the body is restored and recovery made possible. What is required is some means whereby the protective mechanism of the body can be made more sensitive to minor antigenic differences. It may be possible, with modern improved techniques, to augment antibody production through stimulation of antibody forming cells. Many researchers are proceeding along these lines and the real answer to the cancerous process is bound to come in the near future.

Baruah, B. D.: Resistance to cancer; an immunologic approach. I. Indian J. M. Sc. 12:908-918; II. 919-929, Nov., 1958.

The Cobalt-60 Unit in Cancer

Cobalt-60 produces a gamma ray beam equivalent to an x-ray beam of two to three million volts. It is used only in those groups of cases which could not be effectively treated with conventional deep x-ray therapy, provided the tumors were of a type known to be radiosensitive. Among these are carcinomas of the esophagus, bronchus, bladder, posterior part of the tongue, pharynx, postnasal space and extrinsic carcinomas of the larynx and postcricoid region. The low absorption of the supervoltage rays in bone adapts them to the treatment of sarcomas of bone and of adjacent tissue. The cobalt-60 unit has been used for too short a time for any valid estimation of survival rates, but clinical impressions indicate that this supervoltage therapeutic modality will gain a permanent place in radiation therapy. A number of tumors of the upper air passages have completely regressed under cobalt-60 therapy and have not recurred. Many tumors of the bronchus and esophagus have been eradicated. Many useless amputations for bone sarcoma have been avoided by cobalt-60 therapy, and this form of radiation is at present the preferred method of treatment for chondroma.

Strickland, P.: The uses of a cobalt unit for radiotherapy. Postgrad. M. J. 34:419-423, Aug., 1958.

Dystocial Birth of Leukemia

Nine years after Thomas Hodgkin described "some morbid appearances of the absorbent glands and spleen," David Craigie, in Edinburgh, at autopsy of a 30-year-old weaver who had died April 1, 1841 after five days in hospital, found a marked enlargement of the spleen. John Reid examined the blood microscopically and reported "globules of purulent matter." This case of leukemia, probably the first recorded, was not reported until four years later, after Craigie, on March 19, 1845, had participated in the *sectio cadaveris* of a similar patient of John Hughes Bennett. Both cases were published in the *Edinburgh Medical and Surgical Journal*, October, 1845. Bennett's title was "Case of hypertrophy of the spleen and liver, in which death took place from suppuration of the blood." The "veins were full of pus" and the blood was "crowded with corpuscles which exactly resembled those of pus, and could not be colourless corpuscles of the blood" because "we know of no instance where they existed in the amount, or ever presented the appearance, described."

As late as April 3, 1850, Bennett was still referring to this new disease as "white blood," and in 1851 he concluded that "the coloured blood-corpuscle is derived from the colourless one."

Meanwhile, Virchow, in Würzburg, on August 1, 1845, performed an autopsy on a similar case which he described in *Froriep's Notizen* of November, 1845.

Bennett claimed he first saw this report when it was repeated in *Schmidt's Jahrbücher* in 1848.

Virchow described the disease accurately. He opposed Bennett's pus theory and stated that the corpuscles were identical with the colorless blood corpuscles. He attributed their increased number to the enlargement of the spleen, adopting the view of splenic function of Hewson and Donne. For the new disease he proposed the name of *leukhaemia*.

During the late 1840s and early 1850s there was a vehement priority and nomenclature controversy in the medical journals between Bennett, supported by the anonymous L. O. ("probably close to Bennett and an instrument of a more interested party"), and Virchow, supported by his associate Kölliker, by the vituperative Murchison ["It is one thing, Sir, to observe a morbid lesion; it is another to explain its pathological signification"], and by the anonymous E. T.

This was a period of "acrimonious controversy when one's opponent stood naked before the bayonet of the unsheathed tongue and when wounds were rubbed in the bitter ink, stewed with green vitriol, from oak-galls and rusty nails."

Virchow took potshots at Bennett; and Bennett, while asking to "be excused from literary warfare with revolutionary combatants, whose chief weapons are detraction and attacks on character," continued to devote pages to a weak defense of his priority and of his "more accurate" name for the disease, *leucocythaemia*. Virchow's name, *leukhaemia*, according to Bennett and his defenders, is "not only inelegant and cacophonous, but it clashes with the recognized laws of etymology."

One of Bennett's British editor friends even stooped to "casting several personal reflections upon the Professor of Pathology at Würzburg" in a review of Virchow's *Handbook of Pathology*.

Modern, mild-mannered, pussy-footing medical editors, reviewers and writers could learn much from a chronological, blow-by-blow review of this he-man, knock-down, drag-out, century-old brawl —pains at the birth of leukemia. [Ringside score-card bibliography available on request.—Ed.]

Persons of good sense . . . seldom fall into disputation, except lawyers, university men, and men of all sorts that have been bred at Edinborough.

—Benjamin Franklin, *Autobiography*

A Concept of the Etiology of Leukemia

Noel J. Collins, M.B., B.Ch.

Clinical observation of acute leukemia of lymphatic type following immunological procedures started a train of thought which led to the hypothesis that leukemia is an abnormal or pathologically excessive response to an antigen or prolonged antigenic stimulation which may be electively administered or may result from environmental hazards.

The fact that foreign material is eliminated or destroyed *with* antibody production while effete cells of the body's own pattern are broken down *without* antibody production must mean that the scavenging cells can recognize whether the material they are dealing with is of the body's own pattern or something else, that is, that they can recognize the difference between "self" and "not-self." Burnet postulates that during embryonic life the scavenger cells of the reticuloendothelial system by specific contact with "marker protein" develop "recognition units"—units complementary to the marker protein. Late in fetal life antibody production is elicited only by proteins differing from a body "self marker" but nevertheless sufficiently like it to be capable of partial reaction with a "recognition unit." This reaction leads to a modification of the enzymic "recognition units" which multiply and, after transference to the antibody-forming cells, provide a permanent source of self-reproducible antibody. The cells responsible for such active production are necessarily in a state of active protein synthesis. They are the immature plasma cells and lymphocytes. For any long-lasting immunity we must postulate a perpetual growth and reduplication of the cells in which the modified pattern is stored and a constant production and breakdown of lymphocytes.

I suggest the following sequence of events in the genesis of leukemia: In response to an antigen, antibody is formed. This can go on until maximal antibody production has been reached. Thereafter, continued presence of the antigen leads eventually to hyperplasia of antibody-producing cells and consequent exhaustion with the production of abnormal cells, the abnormality being a depletion of some "identity-protein," loss of which confers on the cell the property of unrestricted growth. Adaptation to cells of simpler structure in the presence of a strong immune reaction in bacteria is so familiar that no microbiologist would deny its possibility in animal cells. At some point, if one or more of the continually proliferating cells are to survive the ever increasing antibody production, a biologically effective way is to dispense with one or more modified "tissue identity" proteins.

The normal control of growth depends on a balance between cell division on the one hand and the number of mature cells of that series present on the other hand. The white blood cells of leukemia, being "depleted," cannot be recognized as completely "self" cells, and so the balance is upset and, furthermore, they are liberated from the normal control.

Historically, clinicians have noted the clinical and hematological similarity between acute leukemia and fulminating infections. Indeed Wallbach in 1932 stated that there is no sharp distinction between acute leukemia and fulminating sepsis. The blood picture in pertussis and infectious mononucleosis is still not infrequently confused with that of acute lymphatic leukemia. There is some evidence that leukemia is related to infection. Blanc has shown that the association of leukemia and malaria is more than coincidence and suggests that the sexual forms of the parasite remain for long periods in the bone marrow and spleen where they produce mild prolonged stimulation of hemopoietic tissue finally terminating in chronic leukemia. It has been shown that one of the functions of the spleen is fixation and

From National Children's Hospital, Dublin, Ireland.

storage of antigen where it gives rise to prolonged stimulant effect. The difference between stimulation and irritation is merely one of degree. In those cases in which leukemia is found in more than one member of a family, it is usually lymphocytic and the classical reaction to hematozoic infections, which are the most likely familial infections, is lymphocytic. It is known that leukemia may coexist with tuberculosis and that tuberculosis of the spleen may manifest itself only by a leukemic picture, in this case usually myeloblastic. That this is due to stimulation of reticuloendothelial tissues appears likely. Attempts to transmit leukemia from man to man, even by blood transfusion, have not been successful, and leukemia was never known to be transmitted from mother to fetus. This is not surprising if the concept that leukemia is an abnormal response to antigenic stimulation is correct, unless the antigen was only recently introduced into the donor and was still present in his blood.

Plasma cells and lymphocytes are the chief factors in antibody formation, and for any long lasting immunity we must have a perpetual growth and breakdown of them. During growth of rat sarcoma and Walker carcinoma, certain lymph nodes and spleen show an increasing proportion of plasma cells with diminishing lymphocytes throughout the whole course of tumor growth. Early treatment with cortisone strongly diminishes the plasma cell response.

Beginning natural regression is accompanied by a massive infiltration of the tumor with plasma cells, which appear to be solely responsible for the initial stages of tumor regression. As the plasma cells are not phagocytic it would appear that antibodies produced by them are concerned with this regression.

The only known function of the thymus is the manufacture and perhaps storage of lymphocytes. It normally reaches its greatest size at age 10 to 12 years and then atrophies when the greatest hazards of childhood infections are past. The incidence of leukemia is less in thymectomized than in intact animals.

Temporary improvement may follow intercurrent infections in leukemic patients. Menkin has shown that substances present in inflammatory exudate are capable of causing either hyperplasia or hypoplasia of myeloid marrow. The mechanism governing the release of excess cells in hyperplasia appears to depend on the presence of an intact spleen. Maximal antibody production may well hamper this mechanism.

This consideration is in accord with the constant pathological findings of hyperplastic bone marrow and a large infarcted spleen infiltrated with immature white blood cells in leukemia. Apparently the infarcted spleen is an inefficient regulator of the release of any cells produced, that is if it can be "aware" at all of the "depleted" cells which (according to this hypothesis) are being produced. Jacobson has shown that resistance to induced leukemia can be increased by shielding the spleen or by injection of cells from the shielded spleen.

It may not be irrelevant to recall the clinical similarity between leukemia and Boeck's sarcoid, verruga peruana, and Oroya fever—the last being almost identical with acute myeloid leukemia. Finally on the clinical side is the fact that Hodgkin's disease sometimes follows known infections, pyogenic, tuberculer, syphilitic (and how often unrecognized infections?), and that the nodes involved are those most often involved in daily encountered infections and in precisely the same order of frequency.

The life span of leukemia leukocytes is increased many times, probably about 10 times. They contain five times as much folinic acid as normal cells and have a high content of ribose nucleic and desoxyribose nucleic acids which do not diminish as rapidly as normally.

The ribose nucleic acids are found in the nucleoli and mitochondria of cytoplasm where they appear to be concerned not only with the proliferation of young marrow cells but also with the synthesis of their characteristic cytoplasmic contents, namely, hemoglobin in the red cell series and complex enzyme systems in the spe-

cific granules of the leukocytes. So far as this hypothesis is concerned one of these specific cellular contents is antibody. Cameron has shown that 50 per cent of cellular ribose nucleic acid is in the microsomes, which are important centers of protein synthesis in the growing cell. Mitotic abnormalities are closely associated with different distributions of desoxyribose-nucleic acid, which is an important constituent of chromosomes of the cellular nucleus, where it is presumed to regulate mitosis. As well as being concerned with cell growth and development, nucleic acid complex has been shown to be a stimulator of antibody formation.[22, 23] Carcinogenic radiations lead to changes in chromosomes and genes with disintegration of nucleic acids.[10] Cellular alkaline phosphatase is associated with cell protein synthesis. Leukemia cells show consistently diminished phosphatase activity. This correlates with the demonstration that leukemia cells lack some antigens, namely protein.[11] Burnet and Fenner have shown that the cells responsible for antibody production are necessarily in a state of active protein synthesis. Burchenal has induced remission in some types of leukemia by protein deprivation using 6-mercaptopurine, which is antagonistic to a nucleic acid precursor. Thus it appears that leukemia cells and those concerned in antibody formation are alike in their protein requirements. Engelbreth-Holm has shown that leukemia cells have doubled phosphorus uptake in liver, spleen and lymph nodes. Blood uric acid is raised in leukemia due to breakdown of nuclei of the white blood cells. This appears to occur in the reticuloendothelial system, which is also the system stimulated to produce antibody and may be in a state of hyperactivity. However, new antibody formation is deficient because the antibody-forming apparatus has already been stimulated beyond its maximum capacity to produce antibody, leukemia being the result of this excessive stimulation. To summarize, leukemia cells show increased protein metabolism, but the cells formed are deficient in regard to at least one antigen, that is, protein. The hectic activity of the thyroid in cases of endemic goiter is a further illustration.

Some evidence of excessive white cell destruction has been mentioned; there must be excessive production, at least during phases of absolute leukocytosis. I suggest that, the cells being deficient, there may be, so far as the internal economy is concerned, a lack of white blood cells, similar to the lack of thyroxine often found in the presence of colloid goiter with hyperactivity; that is, the "new" white blood cells may not be recognized at all. Gross, as a result of repeated observations of leukemia in mice, found that carrier mice remain "in good health through their early adult age, because the leukaemic agent, carried by such mice, would exist in an inactive form . . . and therefore harmless for its carrier-hosts. Occasionally, however, and particularly in middle-aged carrier-hosts, the leukaemic agent, prompted by as yet obscure factors, could become activated." I believe that one of the obscure factors is antigenic stimulation as observed by many, including Forkner.

Immunology

The experiments of both Hartley and Burnet strongly suggest that the reticuloendothelial system plays a large part in antibody production. Deutsch and Burnet believe that histiocytes of spleen form antibodies or intermediary products, while de Gara and Angevine have demonstrated that antibody is present in inoculation sites in skin, bone marrow, spleen and lymph nodes earlier than in blood, and persists there longer than in blood; they state that antibody is formed in these sites. With the exception of skin (which, incidentally, does not always escape), these are precisely the organs involved, but with variations in intensity of involvement, in leukemia. Experimentally, it has been possible to produce immunity to leukemia by injection of heat-killed leukemia cells or injection of liver and spleen of immune animals. It seems that liver and spleen contain the protecting agents in appreciable amounts. Hellman and White showed that injection of antigen leads to increase in the

number of germinal centers in lymphoid tissue of spleen and lymph nodes, and stress that germinal centers are not found in fetal tissues and do not appear in young guinea pigs reared in sterile environment. The organs and cells concerned in the scavenging mechanism are also those concerned in antibody formation. Wilson and Miles have shown that above the minimal threshold of antigen the antibody titer is relatively much smaller than the dose required to produce it; eventually a point is reached at which increased dose of antigen produces little or no increase in antibody production. As the same system is concerned in antibody production and scavenging, it is reasonable to postulate that "ceiling" antibody formation may be provoked under certain circumstances at the expense of a scavenger activity; this, if established, would help to account for the increased life span of leukemic leukocytes although their status intermediate between "self" and "not-self" is probably more potent in this respect by liberating them from normal control. The inescapable interpretation of Green's results was the theory that an antigenic change produced in a cell by a carcinogen is the essential primary change in early neoplasia; his theory being that, in order to escape the antibody produced, the cell undergoes adaptation by losing some or all of its "identity-protein," and the more complete the loss the more anaplastic the neoplasm. In accord with Green's hypothesis is the idea, put forward by Miller and Miller, that a tumor cell might be the result of protein deletion. Protein deletion would of necessity alter the antigenic status of any cell. It is relevant to note here in connection with virus leukemia in mice that virus can become an integral part of the nucleoprotein of the infected cell and alter its antigenic properties. Carcinogenic radiations lead to changes in chromosomes and genes with disintegration of nucleic acids; modification of identity-protein is then to be expected. In the case of Hall's parabiotic rats, one developed lymphosarcoma following parabiotic intoxication due to excess antibody to its own identity-proteins produced in the stronger partner. Therefore, to combat this excess antibody some adaptation is necessary, and this adaptation is loss of some or all identity-proteins, which amounts to neoplasm. Oberling states, ". . . not only is it possible to derive sarcomas from leukaemia—but also to obtain leukaemias from a process which for thirty years has always been known as a sarcoma." Engelbreth-Holm also remarks on the similarity of fowl leukemia virus and fowl sarcoma virus.

We have evidence that antibody formation is defective in leukemia and it is likely that the scavenging mechanism is inefficient. Thus the production of even a few cells with altered "identity-protein" might well provide the nidus for neoplasm; further, these cells are unlikely to be inhibited by any specific antibody.

There is no doubt that BCG, for example, produces great cellular proliferation. O'Donovan has demonstrated quantitative and qualitative changes in white blood cells following BCG injection. When this approaches or passes the limits of normal response we may assume that some of the cells produced will be depleted in some way, with alteration of "self-identity," which amounts to neoplasm. It has been demonstrated that leukemia cells lack at least one antigen. This, of course, means that at least one cellular protein complex is altered or lost. Green postulates the same mechanism to account for neoplasm following chronic irritation.

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Book of Current Interest

CANCER. Edited by RONALD W. RAVEN. London. Butterworth & Co., Ltd. 1958. Vol. 1—539 pages. $17.50. [See *CA—Bull. Cancer Progr.* 8:15, Jan.-Feb., 1958.] Vol. 2—641 pages. $17.50. Vol. 3—483 pages. $17.50. Vol. 4—532 pages. $17.50.

The hope expressed in the review of Vol. 1 is fully realized in these additional three of the total six volumes. The completed work will undoubtedly constitute the best single source of current cancer information. In Vol. 2, 33 chapters describe the pathology of malignant tumors. Vol. 3 contains four additional chapters on pathological aspects, and adds sections on the geography of cancer, occupational cancer, cancer education and cancer detection. Vol. 4, in 34 chapters, presents the clinical aspects of malignant tumors by site. All chapters in all four volumes are by experts in the field discussed and are fully documented. Each volume is meticulously indexed.

As an example of the exhaustive coverage given each subject, the topic of this issue of *CA*—the lymphomas and leukemias—is treated in five chapters with a total of 125 pages and 400 references. In addition there are numerous shorter passages on the subject in the more general and the by-site chapters—all accessibly indexed. Similar stores of information on all phases of cancer are contained in the four volumes published so far. No more complete or more current source exists. Editing and bookbinding are superb.

Treatment of Leukemia

Henry D. Diamond, M.D.

Leukemia remains incurable. It is this fact and the evidence of increasing incidence[9, 13, 50, 51, 55, 63] of the leukemias that have stimulated research on a broad front throughout the scientific world.

All methods of treatment should be designed to restore normal morphology and function of the bone marrow and to reverse the clinical manifestations of organ infiltration by the leukemic process. The two main modalities of treatment are ionizing radiation and chemotherapy.

For acute leukemia chemotherapy is the treatment of choice, although x ray is an important adjunct in the treatment of lesions of the central nervous system, bones and kidneys. Two varieties of chemical agents are available for the treatment of acute leukemia—the antimetabolites and the adrenal steroidal hormones and adrenocorticotropic hormone (ACTH).

An antimetabolite is a compound whose chemical configuration differs but little from a normal metabolite such as a nucleic acid precursor, a vitamin or an amino acid. As a result of this chemical similarity these compounds are utilized by the body enzyme systems which they disrupt by virtue of even small chemical differences from normal metabolites. Utilizing this principle Farber in 1948 successfully used a folic acid antagonist in the treatment of acute leukemia.[28] Used at present are the folic acid antagonists aminopterin (4-amino-pteroylglutamic acid) and methotrexate, formerly known as amethopterin (4-amino-N^{10}-methylpteroylglutamic acid). These agents differ from folic acid mainly by substitution of amino for hydroxyl group in the 4-position of the molecule. These compounds cause a relative deficiency of folinic acid (citrovorum factor, leucovorin) throughout the body resulting in somewhat selective damage to leukemic cells.

Aminopterin and methotrexate can be given orally or by intramuscular injection, but the oral administration should be utilized whenever possible. Absorption by either route is equally rapid. In children the usual dose of aminopterin is 0.25 to 0.5 mg. daily; in adults, 0.5 to 2.0 mg. per day. Methotrexate is given to children usually in a daily dose of 2.5 to 5.0 mg., and to adults of 5.0 to 10.0 mg. It should be noted carefully that a five- to ten-fold difference in dosage exists between these two drugs. Abnormal or impaired renal function allows prolonged retention of these agents resulting in greatly increased toxicity. Treatment should be continued until either remission of the leukemia occurs or definite toxicity ensues.[5]

The earliest signs of aminopterin and methotrexate toxicity are manifested as redness and ulceration of the buccal mucosa. The characteristic ulcer has a yellow nidus and a red periphery. Progressive toxicity shows itself by means of anorexia, abdominal cramps, diarrhea and bleeding from the gastrointestinal tract. Buccal ulceration heralds the possibility of ulcerative involvement of the alimentary tract and for this reason should be heeded as an omen to stop therapy. With larger doses and prolonged therapy, depression of bone marrow function occurs, and with severe toxicity there may be epilation.[5]

Patients with acute leukemia treated with folic acid antagonists may need three to 12 weeks of constant therapy to effect complete remission. When remission has been achieved, the physician may either continue maintenance therapy at a dose approximately the same as that used to produce the remission, or he may stop treatment and observe the patient carefully for the first signs of relapse. Relapse may be detected early by frequent exami-

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nations of bone marrow aspirates, and upon the first appearance of hematologic relapse as evidenced in the marrow, therapy should be reinstituted and not delayed until there is clinical relapse.

Control of the disease by treatment with these agents may continue for six months to two years. A recent summary report revealed that 68 per cent of 425 children were improved by folic acid antagonist therapy.[25, 26] Two points, however, should be noted: first, *children* respond, but *adults* seldom do; second, once resistance to methotrexate occurs, cross-resistance to other folic acid antagonists also occurs, though not to purine antagonists nor to ACTH or adrenocortical hormones.[6, 7, 43]

The culmination of studies by Hitchings, Elion et al. of analogues of precursors of nucleic acid as possible therapeutic agents led to their discovery of 6-mercaptopurine as a treatment for acute leukemia.[20, 21, 39] Clarke et al. showed its effect on Sarcoma 180,[10, 11] and Philips et al. reported on its pharmacology.[59] Burchenal and his co-workers reported on its clinical use in children with acute leukemia.[8, 54]

The usual dose of 6-mercaptopurine (6-MP) orally is 2.5 mg. per Kg. of body weight, and in this dosage the drug seldom produces toxicity in children. In adults this or somewhat higher doses may cause nausea, vomiting and evidences of bone marrow suppression. The purine antagonists (6-MP, thioguanine and 6-chloropurine) must be continuously administered to the patient for at least three to eight weeks in order to produce any beneficial effects. Remission, once achieved, should be maintained or prolonged by continuance without interruption of therapy.[5]

Thioguanine (6-mercapto-2-aminopurine) dosage is 2.0 to 2.5 mg. per Kg. daily per os. The dose of 6-chloropurine (6-CP) is 20 mg. per Kg. by mouth daily and produces remissions in children at about the same rate as 6-MP. In adults, however, 6-CP produces perhaps a somewhat better remission rate than 6-MP.[22, 23] When resistance develops to one purine antagonist such as 6-MP, it develops likewise to thioguanine and to 6-CP. No cross-resistance, however, to the adrenal corticosteroids or ACTH occurs, nor to the folic acid antagonists.[8]

Some glutamine antagonists have affected leukemia favorably in experimental animals; these are azaserine (O-diazoacetyl-L-serine) and 6-diazo-5-oxo-L-norleucine (DON).[2, 4, 12, 14, 17, 18, 19, 64, 68]

In humans, especially children, these agents given alone show no beneficial effect on acute leukemia. When given together with 6-MP, however, they may be of some value. 6-MP presumably prevents the incorporation of a hypoxanthine-containing precursor into nucleic acid, whereas azaserine and DON prevent the amination of formylglycine amide ribotide to formylglycine amidine ribotide, a step in the de novo synthesis of the purine ring. Thus sequential blocking of the synthesis of purine polynucleotides by the combined use of these agents (6-MP with azaserine and 6-MP with DON) seemingly is rational. A cooperative study is now being done by a number of investigative groups to determine whether there is any real advantage of combination therapy over 6-MP alone.[5, 24]

ACTH and the adrenocortical steroid hormones are useful in treating acute leukemia, especially when the production of rapid remission is crucial.[5, 29, 30, 58] Remissions, so induced, are not so long-lived, generally, as those produced by folic acid antagonists and purine antimetabolites. ACTH seems to act most rapidly and may be given most effectively by the continuous intravenous drip of 25 to 50 mg. per day. The adrenal hormonal agents can be given orally, and prednisone seems preferable at present. In children the usual dose is 50 mg. per day in divided doses, and for adults 100 mg. per day similarly administered. The undesirable side effects are too well known to warrant further discussion. These agents will cause remissions as high as 70 per cent in children, and to some degree also in young adults. Adults over the age of 30 with acute leukemia are rarely improved by these agents, though they should be tried in the profoundly and acutely ill patients regardless of age.

In his survey of the literature, Tivey found that the median survival time of 218 children with relatively untreated acute leukemia was 3.9 months, as compared with 12.4 months in 184 consecutive patients (children) treated with the various antimetabolites, and ACTH and adrenocortical hormones at Memorial Center, definitely indicating prolongation of survival by these chemotherapeutic agents. In the treated adults studied at Memorial Center by Ellison,[23] there was a small but perhaps insignificant increase in survival time. Remissions in adults can offer them periods of normal existence. For this reason, and the more objective reasons in the case of children, *all* patients with acute leukemia should be treated with these available compounds.

The treatment of the chronic leukemias has an interesting history as regards the older chemical agents as well as the newer ones that have been developed with the advent of cancer chemotherapy.

In this country at the turn of the century, Pusey and Senn pioneered the therapeutic use of x rays in chronic leukemia.[60, 61] Today, high voltage and supervoltage x rays are available for treatment of patients with chronic myelocytic and lymphocytic leukemia. A dose of 50 to 100 r (in air) to anterior and posterior splenic fields, alternating ports daily until each field has received from 300 to 600 r (in air), will not only shrink the enlarged spleen in chronic myelocytic leukemia, but will reduce the elevated leukocyte count. The peripheral node-bearing areas in the patient with chronic lymphocytic leukemia may be treated effectively with x rays, using increments of 100 r to each field until 200 to 400 r (in air) has been delivered to each portal. Similar therapy to the spleen and liver will result not only in reduction of spleen and liver size, but also in leukocyte count as well. Total body radiation from external sources such as x rays or internal radiation by radiophosphorus may achieve satisfactory remission also.[15, 16, 56]

One of the oldest chemical agents, still respectable for the treatment of chronic myelocytic leukemia, is arsenic.[32, 49] The dosage schedule is usually five minims three times daily, increasing one of the doses by one minim each day until 10 to 12 minims three times daily are being taken. Then the procedure is reversed and each day one dose is diminished one minum until a maintenance level of five minims three times daily is once again achieved. Arsenic is administered in the form of potassium arsenite (Fowler's solution). Toxicity is manifested by nausea, vomiting, diarrhea, keratoses or skin pigmentation.

Benzol may be given orally to patients with chronic myelocytic leukemia in doses of 4.0 cc. in olive oil daily, but it is rarely used in this country.[40,44]

In 1946[57] urethane (ethyl carbamate) was shown to be effective for reducing leukocyte count to normal and inducing clinical remissions in patients with chronic myelocytic leukemia and, later, in chronic lymphocytic leukemia[38] as well. The usual dose is 3.0 gm. per day by mouth in divided doses. Considerable anorexia, nausea, vomiting and lethargy may be produced, limiting the feasibility of the use of this drug.

The polyfunctional alkylating agents can be used to treat chronic granulocytic leukemia as well as chronic lymphocytic leukemia. Nitrogen mustard (HN2) (methyl-bis-[beta-chloroethyl] amine hydrochloride) in a single dose of 0.4 mg. per Kg. intravenously in chronic myelocytic leukemia, or 0.1 mg. per Kg. intravenously daily for two to four days in chronic lymphocytic leukemia will induce hematologic and clinical remissions lasting two to six months.[41] Nausea, vomiting and the annoyance of intravenous administration are drawbacks to the use of this agent.

Triethylene melamine (TEM) given orally or intravenously to patients with chronic leukemia causes less nausea and vomiting than HN2. The oral dose is 2.5 mg. daily for two to four days; the intravenous dose is 0.04 mg. per Kg. daily for three days. Leukocyte depression and nodal and organ enlargement are reduced by this agent.[42, 47]

Triethylene phosphoramide (TEPA)

and triethylene thiophosphoramide (thio-TEPA) are chemically related to TEM and have about the same therapeutic value and toxicity as TEM in chronic leukemia.[27, 62, 63]

Myleran (Busulfan*), a more recent polyfunctional alkylating agent,[33, 35, 37] seems to be the chemotherapeutic agent of choice in the treatment of chronic granulocytic leukemia. It is effective also in chronic lymphocytic leukemia when administered over a sufficient period of time.[45, 53] The usual oral dose in chronic myelocytic leukemia is 4.0 to 6.0 mg. daily. In this dosage, nausea and vomiting occur rarely. Little hematologic or clinical effect is apparent before three to four weeks. When remission occurs, maintenance therapy with 2.0 mg. per day every other day or twice weekly is indicated.

An epoxide, di-epoxypiperazine, an alkylating agent, has been demonstrated to affect beneficially chronic myelocytic and lymphocytic leukemia.[46, 52]

Whenever any alkylating agent is employed in the treatment of chronic leukemia, it is important to check the *entire* hemogram frequently because platelets as well as leukocytes are depressed by these agents.

Chlorambucil (CB 1348, Leukeran*) has been shown to be very effective orally for the control of chronic lymphocytic leukemia in a daily dose of 0.2 mg. per Kg.[1, 3, 34, 36, 67] When remission is achieved, continued therapy with 0.1 mg. per Kg. daily is important to maintain and lengthen the remission time.[53] This compound in higher doses over appropriate periods of time will ameliorate chronic myelocytic leukemia effectively.[45, 53]

The folic acid antagonists have been shown to have no particular beneficial effect on chronic leukemia short of the appearance of severe toxicity, but the purine antagonist 6-MP is an effective agent for the treatment of chronic granulocytic leukemia; especially is it indicated in the late stages of this disease and in the phase of myeloblastic crisis.[5] The dose is the same as that for acute leukemia and maintenance therapy after remission has occurred is important.

The adrenocortical hormones and ACTH are effective in the treatment of chronic lymphocytic leukemia, especially in those patients with acquired hemolytic anemia or thrombocytopenia. Prednisone, 30 to 60 mg. daily in divided doses, will usually bring about clinical and hematologic remission, but occasionally doses in excess of 100 mg. per day may be necessary, especially when it is desirable to alter a concomitant hemolytic state.[5]

Whether these hormonal agents alter the course of chronic myelocytic leukemia favorably or unfavorably is still debatable.

The total care of the patient with leukemia should be stressed. Hemorrhage and infection are the two main serious complications in leukemia. Septicemias, especially involving antibiotic-resistant organisms, occur only too frequently.[5] Severe anemia should be treated with transfusions of blood, preferably packed red blood cells.

Leukemic involvement of the meninges of the central nervous system may be treated beneficially with x rays or intrathecal methotrexate.[69, 70] The entire cranium can be irradiated through opposing lateral fields on 250 kv., half-value layer of 2.0 mm. of copper, at 50 cm. to 70 cm. target-skin distance. The daily dose is gradually increased, starting with 50 r (in air) daily for two days, then 100 r (in air) daily for the next two days, 150 r (in air) for the next two days, and so on, until the meningeal signs subside or the leukocyte count of the cerebrospinal fluid falls below 100. Usually, the tissue dose necessary to achieve therapeutic results is 300 to 500 r delivered over five to 10 days.

The intrathecal dose of methotrexate, as reported by Whiteside et al., is 0.5 mg. per Kg. every five days for a total of three injections. Since high levels of the drug are achieved by this technique, this form of treatment is effective in some patients who were previously resistant to methotrexate. Oral administration of methotrexate should be stopped during intrathecal therapy.

Hyperuricemia and hyperuricuria,

*Trade name—Burroughs-Wellcome & Co.

which may occur, should be anticipated and treated vigorously with fluids so that a high urinary output is achieved. Dialysis with the artificial kidney may be life-saving at times.

The physician must realize that in chronic leukemia no treatment may be indicated if the patient feels entirely well. He should also remember that he is not treating the white blood cell count but rather the patient.

Recently, with the advent of bone marrow transplants, autologous and homologous, in addition to transfusions, after total body irradiation in order to allow "take" of the transplants, an exciting chapter has been added to the story of the treatment of leukemia.[31, 48] Much work remains to be done in this sphere, but theoretically this approach holds great promise as a definitive method of treating leukemia as well as repopulating a bone marrow virtually wiped out by a lethal dose of an antimitotic chemotherapeutic agent.[31, 48]

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The Smoking Physician

L. Henry Garland, M.D.

[*1. At a recent Regional Meeting of the American College of Physicians a panel of prominent, and smoking, oncologists was asked:*

Q—How do you reconcile your smoking cigarettes with your expert knowledge of the etiology of cancer?

A—We have now reached an age when the harm has been done. If we were going to develop cancer of the lung we already have it. Therefore, we might as well continue to smoke and enjoy ourselves.

They could have added, but did not, that several authoritative studies have shown that the smoker who stops—at any age and after any number of years of smoking—definitely lessens his chances of getting lung cancer.

2. Radio interview:

Q—I notice, Dr. Garland, that you smoke. What about smoking and its relation to cancer?

A—I'm sure it's bad for me. I'm sure it will shorten my life. I won't live to be 150; I'll only be about 125, I'm afraid.

Q—And you're going to give up those last 25 years so you can enjoy the weed?

A—I am.

After this interview Dr. Garland was asked to prepare for CA *a summary of the several rationalizations by the smoking physician, and to include a frank statement of the physician's duty to the patient. His article should be read in conjunction with that of the nonsmoking physician, p. 62. Comments invited.—Ed.*]

Swift, in his *Critical Essay upon the Faculties of the Mind* observed that "there is nothing in this world constant but inconstancy." The bard of Avon had it otherwise, comparing consistency to the fabled jewel. This matter comes to mind in attempting to summarize some current attitudes of the physician toward the smoking question.

As with so many other questions, there would seem to be three possible answers: "Yes," "No" and "I don't know." Physicians who act and say "*Yes*" to smoking agree with Oscar Wilde, who observed, in *The Picture of Dorian Gray*, that "a cigarette is the perfect type of a perfect pleasure. It is exquisite, and it leaves one unsatisfied. What more can you want?" He agreed with Stevenson who noted that "there are no such pipes to be smoked as those that follow a good day's march; the flavor of the tobacco is a thing to be remembered, it is so dry and aromatic, so full and so fine." This doctor feels that the small percentage change of bronchial neoplasm is acceptable in the light of the tremendous pleasure given by the weed. He knows that about two out of every thousand male heavy smokers, that is, men who smoke forty or more cigarettes every day for twenty or more years, are pretty sure to develop primary lung cancer in EACH YEAR between the ages of 55 and 75. He is fatalistic—and feels that the hazards of such pleasures as ice cream are acceptable even in the face of atherosclerosis, as protein-filled banquets in the face of gout, and as swift access to the duck club by automobile in the face of highway fatalities.

The "*No*" physician is either one who is sensible enough never to have developed

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the untidy habit, or strong enough to have reformed. He agrees with King James I that tobacco is "a branch of the sin of drunkenness, which is the root of all sins." He remembers Selden, in his essay on *Table Talk:* "Tobacco—that which is the great pleasure of some men; at first they could not abide it, and now they cannot be without it." He knows that, in addition to causing an increased prevalence of lung cancer in susceptible men more than 50 years of age, excessive use of tobacco is undoubtedly a factor in cardiac disorders in certain persons, tends to aggravate peptic ulcer in some types of adults and is associated with an increased incidence of cancer of the lip, tongue and larynx in a small percentage of men. With such hazards constantly in mind, with no taste for the black and oily tars, the clouds of smoke, the disturbed olfactory appreciation of finer foods and beverages, he readily discourages smoking at any age.

Finally, and most difficult, is the physician who *"Does not know."* He remembers that, just prior to the turn of the century, tobacco was blamed for tuberculosis. He notes that examinations of the lungs of heavy cigarette smokers reveal precancerous changes in parts of the trachea and main bronchi where primary lung cancer is relatively uncommon. He knows that evidence obtained on animals is not directly translatable to man. He knows that the controls in any large population study are of debatable quality; it is virtually impossible to match two groups of adults in temperament as well as age and habits. He wonders why primary lung cancer should be twice as common in British men as in American men, although cigarette consumption is only half as great in England as in the United States. He notes the paradox in the figures relative to inhaling and lung cancer, and is interested in the increasing incrimination of other air pollutants as significant cocarcinogens in our smog-laden cities. These "chinks in the statistical armor" were summarized by Macdonald and do not need to be dwelt on further in this homily.

What then should we teach the doctor to teach our teen-agers? It seems to me we should teach him to recommend moderation in all things, in eating, in drinking, in exercise and in sleep. He should teach teen-agers that smoking is not a sign of manliness or courage. True contentment comes from doing something for others and not for ourselves. Life owes us little; we owe it everything. Happiness comes from squandering ourselves for a purpose. He should teach teen-agers to seek the acquisition of a purpose or aim, and to remember that a productive life is much more important than a long one. Indeed, he might even teach such unpalatable truths as the fact that war is commoner than peace, and discontent the first essential of progress. If, as is likely, the teen-ager has already started smoking, he could try to help him place the hazards in proper perspective, always remembering that, other things being equal, a cheerful disposition is more important than a perfectly functioning cardiopulmonary apparatus.

He may even remind the teen-ager of the British physician who got so irritated at all of the articles he read about smoking that he gave up—reading.

Reference

Macdonald, I.: Contributed comments. I. Chinks in the statistical armor. CA—Bull. Cancer Progr. 8:70, 1958.

Precept or Example

The only rational way of educating is to be an example—if one can't help it, a warning example.

—Albert Einstein

The Duty of the Physician Towards His Patients in Regard to Cigarette Smoking

David M. Spain, M.D.

The practicing physician is currently faced with the serious responsibility of advising and educating his patients (males, females, adolescents, teen-agers and adults) on the effects of cigarette smoking on their health. The overwhelming mass of substantiated facts no longer permits him to be jocular about or remain aloof from this problem. The cynical attitude towards life in this atomic bomb and cold war era and the pseudosophistication fostered by the commercialism of some of our popular means of entertainment and communication cannot obscure the simple and homely principles upon which the ethical and scientific foundations of the practice of medicine are so firmly built. These principles, equally valid for the horse and buggy doctor as for the modern city practitioner, are that prevention of disease comes first; failing this, cure and eradication are tried; or if this is impossible, one then palliates, prolongs life and relieves pain and suffering. To depart from these principles is to subvert the morality upon which the modern practice of medicine is based. Nor is it within any physician's province to assume the role of a supreme being and decide which diseases he is to prevent and which he is to permit his patients to die from.

An event of staggering importance has taken place in the field of cancer research. For the first time knowledge is available which, if properly utilized, can substantially reduce the incidence of one of the major forms of cancer, namely, bronchogenic carcinoma.

With every other advance in medicine the physician has made it his duty to inform himself of its value and use (poliomyelitis vaccine, diphtheria antitoxin, penicillin, etc.). So must he now accept the responsibility of adequately informing himself of the facts and their proper utilization as regards the effect of cigarette smoking on health.

Every student of medicine knows that there are three tried and tested approaches into the nature and cause of a disease. These methods are statistical (epidemiological), experimental (test tube and animal) and human (clinical, physiologic and anatomic).

In 1956 a study group consisting of several scientists and physicians was organized under the sponsorship of the American Cancer Society, the American Heart Association, the National Cancer Institute and the National Heart Institute. Their assigned task was to accumulate, evaluate and analyze, with first-hand observation wherever possible, all significant reports, experiments and investigations on the subject of smoking and health. The men in this group had no preconceived ideas, were objective, some smoked and some did not, and had no particular axe to grind. They spent a year critically analyzing and assessing the information along the three lines of approach to disease previously mentioned. In June, 1957 this study group issued a report which appeared in *Science*.[1] They found that every statistical study conducted by authoritative, reliable and well recognized investigators arrived at essentially the same results. In over 16 such independent studies carried on in five countries, it was noted that lung cancer occurred up to 15 times more frequently among cigarette smokers than among nonsmokers. It is of the utmost significance to note that the medical literature did not contain a single well controlled statistical or epidemiologic study that refuted or negated these find-

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ings. In the experimental field numerous chemical carcinogens have been repeatedly extracted from tobacco smoke condensate, regardless of the type of cigarette used. Furthermore, carcinogens in this tobacco smoke condensate consistently produced malignant tumors in experimental animals. This has been repeated in several of the leading cancer research laboratories in the country. Investigation on human material reveals that detailed microscopic studies on thousands of sections from human bronchial mucosa demonstrated a clear-cut relationship between the earliest anatomically recognized stages of cancer and the cigarette smoking habit. In short, all recognized avenues of approach complement each other and support the only conclusion possible, namely, that "the sum total of scientific evidence establishes beyond reasonable doubt that cigarette smoking is a causative factor in the rapidly increasing incidence of human epidermoid carcinoma of the lung."

It has been calculated that on a lifetime basis one of every ten men who smoked more than two packs of cigarettes a day would die of lung cancer, whereas the comparable risk among nonsmokers was only one chance out of 275.

Opposing these solid, well controlled studies and tremendous accumulation of scientific evidence, which has been produced by the practicing physician's own peers and accepted by his own health agencies and major research foundations, as well as by the national health agencies of other countries, are the newspaper handouts and public relations releases manufactured by a handful of men in the employ of the Tobacco Industry Research Committee. On the one hand are the facts produced by the scientists themselves and on the other hand are the opinions by sideline observers produced for the purpose of setting up a smokescreen and maintaining the figment of controversy.

The facts and conclusions are clear. It now becomes the urgent responsibility of the practicing physician to acquaint himself immediately with the full report of this study group.[1] He should also be cognizant of the fact that all subsequent studies, reports and experiments confirm and extend the original conclusions. Having thus informed himself, the physician must now practice the best form of medicine he is aware of—preventive medicine. He must inform, advise and guide his patients to the best of his ability and time in this matter. This advice must also take into account the accumulating evidence of the relationship between smoking and other forms of cancer and certain forms of heart disease.

That cigarette smoking is a pleasurable and well entrenched habit cannot justify failure on the part of the physician to fulfil his obligation. He certainly does not shirk from the painful task of advising the parents of a ten-year old child that a leg amputation is required for a malignant tumor. He certainly does not advocate the smoking of opium because it may be pleasurable to certain individuals. The argument that smoking is the risk one incurs in the process of living is a feeble excuse. After all, driving a car is part of the modern living process, yet there are penalties for unsafe driving and legislation against drunken driving. The argument that the damage has already been done—why stop smoking now—is not in accord with recent studies, from which it appears that cessation of smoking (even after many years) substantially reduces the risk of developing bronchogenic carcinoma.

Surely, the physician should spend at least as much time in informing and advising his patients on this subject as he does in giving transfusions and stimulants in order to prolong life for a few agonizing days in terminal and inoperable cancer cases and in consoling the bereaved family. Unquestionably, his efforts will prove medically more rewarding.

The approach to the adolescent and teen-ager is of prime importance because in this group the habit has as yet not become so well fixed. To achieve meaningful, lasting and optimum results the physician must probe into the hearts and minds of these young individuals in order to comprehend fully why they smoke. He must have insight himself into this prob-

lem and be prepared to impart this understanding to the adolescent and teen-ager that the question of smoking is not a moral one but purely and simply a problem of their health. He should recognize and be prepared to destroy the false idols which motivate adolescents and teen-agers to smoke—such idols as "feeling big; social acceptance, being a big-shot, looking sophisticated, etc." He must be prepared to counter their feeling of remoteness and lack of personal identification with individuals over 40 years of age who develop cancer. Fortified with the facts of the case, proper understanding and with the devotion of the proper time and sincerity, gratifying results will be forthcoming. If necessary, as an example, he must even stop smoking himself.

It surely is little comfort to the wife, children and the doomed father or husband in the terminal death agony of bronchogenic carcinoma to say that he is merely paying the price for years of having indulged in a so-called pleasurable habit. The practicing physicians in this country fortified with the available knowledge and acting in unison can, within a few years, reduce this major form of cancer to a minor problem.

The best traditions of American medicine permit no alternative to this concerted effort.

Reference

1. Joint Report on Smoking and Health. Study Group on Smoking and Health: Science 125:1129-1133, 1957; Section on Lung Cancer. CA—Bull. Cancer Progr. 8:57-61, 1958. [Available on request.—Ed.]

Not As I Do

The physician "from time to time will find it his duty to advise patients not to smoke. The degree of emphasis with which he conveys that advice will be influenced by his own habits, but there are some circumstances in which he must give that advice even if he himself is a chain-smoking inhaler."

Doggart, J. H.: Practitioner 182:204-211, Feb., 1959.

The group of lesions classified as the malignant lymphomas by many American pathologists represent partial pictures based on the study of isolated lesions of lymph nodes of patients who may have more generalized and leukemia-like conditions. The fact that the malignant lymphomas may appear in aleukemic and leukemic forms, depending partly on the time of study of the patient and partly on the extent of the study and no doubt partly on the nature of the pathogenic process itself, indicates that there is a fundamental relationship between the malignant lymphomas and leukemia, at least in the way the tissues react to varied and possibly unrelated stimuli. Our present ignorance of the nature of these stimuli emphasizes the provisional nature of the entire concept of the malignant lymphomas as a disease entity.

Berman, L.: The malignant lymphomas. In Rebuck, J. W.; Bethell, F. H., and Monto, R. W., Eds.: The Leukemias: Etiology, Pathophysiology, and Treatment. New York, Academic Press, Inc. 1957; p. 210.

CANCER CLINIC

Consultation by Correspondence

Replacing the usual Cancer Clinic in this issue is the following account of a medical problem presented in a letter from a 42-year-old male physician and of the opinions of the various consultants to whom the letter was referred.

Physician's letter:

In 1943, when I was 27 years of age, I began to notice a feeling of fullness after meals accompanied by nausea and occasional vomiting. At that time my weight was 160 lbs. and my height was 5' 10". Tests revealed that there was no free hydrochloric acid in the stomach following histamine and that there was a questionable filling defect at the pylorus. Surgery was recommended and at operation a Grade III, nonspecific ulcerative gastritis was found. A posterior Polya resection of three fourths of the stomach was done. During the subsequent seven or eight years I lost 20 lbs. in weight as a result of a severe dumping syndrome and esophagitis.

At the age of 36 years I developed what appeared to be a hypochromic anemia. Although blood smears did not show any changes characteristic of pernicious anemia, I was put on crude liver extract, 1 cc. weekly, and the results were favorable. I am now receiving 50 micrograms of B_{12} monthly and have a completely normal blood picture.

Eight months ago I developed brownish blotches on both legs; this was diagnosed as Schamberg's disease.

At present my weight is 140 lbs. and I feel well except when I am under tension, which seems to produce an esophagitis. I have had an upper gastrointestinal series of x rays every year since 1943 and they show a normal mucosa and functioning stoma. No gastroscopic examination has been done since the operation.

Six months ago a Schilling test indicated less than 1 per cent absorption, suggesting the possibility of pernicious anemia, although the bone marrow was not examined and the blood picture has been normal. Since the operation in 1943 there has been no evidence of free acid following the histamine test.

Several insurance companies have refused to insure me because of the high incidence of cancer of the cardiac portion of the stomach in achlorhydric patients.

I would like to have answers to these questions:

1. Since I am having an upper gastrointestinal x-ray series yearly and occasionally twice yearly, am I being exposed to excessive radiation over the years?

2. Assuming I have pernicious anemia (although no other member of my family has it) would this disease increase the likelihood of my developing cancer in the remaining cardiac portion of the stomach? Should I have special cytologic and gastroscopic studies every year?

3. Can a biostatistician give me data on the following:

   a. What per cent of cancer develops in the pyloric and lower portion of the stomach?

   b. What per cent in the fundus and cardia?

   c. What per cent in patients with pernicious anemia, and in what location?

   d. In view of the fact that three fourths of the stomach is missing, what are the chances of developing carcinoma in the remaining portion of the stomach?

Radiologist:
Dr. Antolin Raventos

The effects on human adults of repeated exposure of a portion of the body to small doses of ionizing radiation such as described are not accurately known. There is reason to believe that such exposure may not be innocuous, however; in other words, some of the injurious effects of radiation which are well established at higher dose levels may actually have no threshold and thus may be a hazard, even though of low probability, at the exposure levels encountered in diagnostic roentgenology. For this reason, it is best to consider *any unnecessary* exposure to be excessive. The decision as to whether any medical procedure is or is not necessary should be made by balancing the probability of benefit to the patient against the risk of the procedure and its cost in time and money. Enough is known of radiation hazards to indicate that the risk involved in semiannual roentgen examinations of the gastrointestinal tract is probably quite small if the examinations are done properly. The possible risk should be a factor, but only a very minor factor, in the doctor's decision as to whether to continue this practice.

The equipment and technique used in the roentgen examination are of great importance. A fluoroscope can be adjusted to deliver as little as five r per minute at the table surface and still perform quite satisfactorily for gastrointestinal work. Every fluoroscope should be checked periodically for radiation safety by two radiological physicists. Examination of the stomach with a properly adjusted fluoroscope might be expected to expose a few square inches of skin to a dose of several roentgens, the stomach itself to one or two roentgens, adjacent organs to a lesser dose, and distant organs to only very small amounts of radiation. By working rapidly and with small shutter openings, an experienced radiologist can reduce the patient exposure to a small fraction of that which would be delivered by a less exacting technique. Since the radiation dose incurred in any fluoroscopic examination is so greatly dependent upon these factors, it is of special importance that the highest standards of radiological practice be employed in the performance of "routine" examinations when it is considered necessary to repeat them periodically for the same individual. The radiation dose is further reduced in periodic re-examinations of the stomach by limiting fluoroscopy to the stomach itself and limiting films to a few positions carefully chosen for comparison with the patient's previous films.

The frequency with which the gastrointestinal x rays should be repeated depends upon the benefit to be expected. It can hardly be doubted that one gastric cancer is more dangerous than many properly done gastrointestinal x-ray studies, perhaps even as *many as one a month for life*. The real questions are: Does this individual have a significant predisposition to gastric cancer? Is the gastrointestinal x ray appreciably better for the detection of curable stomach cancer than methods which do not employ radiation? What is the likely interval between the time when a stomach tumor becomes detectable and the time when it becomes incurable? I am not competent to answer these difficult questions and I hope that the other consultants will discuss them. For the second and third questions, however, I suspect that there is no universally applicable answer. The effectiveness of a diagnostic method depends upon the individual using it. All of us are aware of cases in which a tumor was diagnosed roentgenologically but was not seen gastroscopically, for example, and also of the converse occurrence. Different physicians, by reason of training and experience, place differing degrees of reliance upon the various diagnostic procedures available to them. I think that the patient should best be guided by the counsel of the doctors to whom he has entrusted his own care, even if it should not fully agree with recommendations from other localities, and that he need not be greatly concerned about the radiation exposure involved in whatever studies they consider necessary.

Surgeon:
Dr. Claude R. Hitchcock

Initially this patient demonstrated the problem of achlorhydria and a prepyloric lesion which was appropriately treated by subtotal gastrectomy. From the diagnosis of the pathologist I would infer that the patient has something in excess of an atrophic gastritis, probably an inflammatory type of gastritis, with superficial ulceration of the mucosa. This would not preclude the presence of atrophic changes in the gastric mucosa, however, in the fundus and upper portion of the body of the stomach. In terms of the surgery performed one might suggest that if a true Polya resection was accomplished, the undue difficulty with the dumping syndrome might have been somewhat lessened if there had been a Hofmeister treatment of the lesser curvature and a somewhat smaller stoma for the gastroenterostomy.

It is apparent that the patient developed the hypochromic anemia at the age of 36, nine years after surgery. The true nature of the anemia is in doubt at this point in the history, but probably the patient suffered only a nutritional deficiency at that time.

The Schilling test, performed in this instance five and a half years after the hypochromic anemia was diagnosed, indicated less than 1 per cent absorption. In our clinic this would be good evidence for a severe deficiency of intrinsic factor in the remaining gastric pouch. Under these circumstances pernicious anemia should be strongly suspected. We have, however, noted several patients who failed to excrete any orally administered radioactive vitamin B_{12} (when they were being studied as candidates with histamine-fast achlorhydria only) and in whom there was no clinical evidence of pernicious anemia. Under these circumstances the addition of intrinsic factor orally with the radioactive vitamin B_{12} resulted in normal absorption from the gastrointestinal tract and the excretion of normal amounts of radioactive material in the urine. On this basis we believe that some patients with true achylia gastrica, demonstrated in this manner, but in whom no clinical evidence of pernicious anemia can be found, may have a predilection for gastric cancer similar to those patients with clinically evident pernicious anemia. At the present time this hypothesis can not be positively substantiated.

During a 12-year study of patients with achlorhydria, hypochlorhydria and pernicious anemia, we have established the fact that patients with pernicious anemia have a chance of developing gastric cancer 21.9 times greater than that of normal persons in the same age range of the population. In patients with achlorhydria and severe hypochlorhydria the chance of developing gastric cancer is 4.5 times greater than it is in normal persons of the same age range. On the basis of these findings I believe that the patient in question has a significantly increased chance of developing carcinoma in the remaining fundic portion of the stomach, and this is important enough to warrant gastroscopic studies every four months.

In fact, I believe it is impossible to determine from repeated roentgenograms anything of real significance regarding the character of the mucosa and would suggest the value, in the case at hand, of gastroscopic studies every three months and of occasional biopsies of the mucosa. It would seem wise to alternate gastroscopic examinations with gastrointestinal x-ray series and thereby reduce the amount of irradiation to which this patient would be exposed over the remaining years of his life.

I once subjected a group of interesting patients with gastric polyps to gastroscopic examinations every three months for six years and was delighted to note the ease and good humor with which these people complied with the demands of this vigorous approach. The well-trained gastroscopist causes little discomfort for his patient and the procedure is safe in his hands.

Studies in our clinic have revealed that patients who have a normal mucosa in the body and the fundic portion of the stomach, and who have either a segmental resection or a subtotal gastrectomy with Billroth I or Billroth II reconstruction, do

not develop pernicious anemia clinically and are not deficient in intrinsic factor as determined by the Schilling test. However, those patients in our clinic who have had resection of the entire fundus and body of the stomach, with esophago-antrostomy reconstruction of the gastrointestinal tract, have gone on to develop the picture of pernicious anemia and Schilling tests have indicated the absence of intrinsic factor in the remaining antral pouch. This could truly be considered an induced pernicious anemia because the patient has had the intrinsic factor-producing portion of the stomach removed at surgery. Needless to say, those patients in our clinic who have had total gastrectomy and who have survived for a significant period have also inevitably developed pernicious anemia.

Our experience reveals that approximately 50 per cent of gastric cancers develop in the prepyloric or antral area. In our group of patients with pernicious anemia cancer develops in 5.2 per cent of the over-all number of cases. This figure is 21.9 times greater than the figure for the incidence of cancer in patients of comparable age groups who do not have pernicious anemia. In patients with pernicious anemia who develop gastric cancer, the lesions have the same general distribution with the majority of lesions appearing in the prepyloric area or the antrum. In view of the fact that the patient in question has had the distal three fourths of his stomach resected, it is difficult to state what the chances are that he will develop a carcinoma in the remaining fundic portion of the stomach. Probably all that can be said here is that if the patient had had a resection of the fundic and body portion of the stomach with an esophago-antrostomy, he would have, perhaps, a slightly greater chance of developing cancer than he has under the circumstances as they now stand. I do not believe exact figures can be placed upon this probability.

In regard to a plan for the future in the case of this patient I would advise a gastroscopic examination every four months and an upper gastrointestinal series of x rays every 20 to 24 months. Biopsies of any suspicious areas of the mucosa should be taken and routine biopsies should be done every two years. The patient should, of course, continue therapy with vitamin B_{12}.

Oncologist: Dr. Charles S. Cameron

It seems very difficult to be sure that this man does have pernicious anemia. I have found no advice which indicates how this matter can be resolved and my own feeling is that the doctor's statement that the blood picture is always normal means nothing since he concedes that liver and B_{12} have been used constantly for 15 years. What would the picture be if he were to discontinue this medication for a test period?

As to the x-ray exposure, my feeling is that this yearly gastrointestinal x-ray series constitutes an undesirable degree of irradiation. I don't know what "excessive" is because, presumably, what is excessive for one person is tolerable for another. Even though it is undesirable from the point of view of increasing the patient's susceptibility to—say, leukemia, the question whether it is relatively desirable depends upon the likelihood of carcinoma in the remaining portion of his stomach, which likelihood is again going to be influenced by whether he has pernicious anemia or not. Ergo, on a logical basis, the question is unanswerable. Even assuming he has pernicious anemia, I would think that the chances of his developing carcinoma in the cardiac portion of his stomach do not justify annual gastrointestinal x-ray series. I am inclined to feel that they do not warrant special cytological and gastroscopic studies yearly. No one seems to know yet what the cytological evolution of cancer of the stomach is. It may prove to be a protracted affair in which case cytologic studies of the gastric contents of this patient might be reasonably scheduled biannually.

Dermatologist: Dr. Frank C. Combes

I am not qualified to comment on many of the problems presented by this patient but am glad to give my opinion on a few. First, if he has Schamberg's disease, it is nothing to worry about. It is not related

to pernicious anemia, to ionizing radiation, nor to any type of cancer. It occurs usually in young adults, is of unknown cause, is frequently misdiagnosed (although it has a definite histologic picture) and reaches a certain stage and remains static. It is not associated with any blood or bone-marrow disturbance.

Second, every series of x-ray examinations of the upper gastrointestinal tract exposes the skin to approximately 20 roentgens. Therefore the patient has already had many times the safe limit. I certainly would stop the practice of repeated gastrointestinal series because I fail to see what purpose they serve. I would be interested in his fecundity and would suggest a spermatozoon count.

Biostatistician:

Dr. B. Aubrey Schneider

The distribution of stomach cancer by location varies somewhat, depending on the proportion of cases assigned to such categories as "entire stomach" or "extensive involvement." In the latter cases it is difficult to determine the exact location of origin. In a series of 493 cases of carcinoma of the stomach studied by La Due, Murison, McNeer and Pack, the following distribution by location is noted: pylorus, 34 per cent; fundus, 22 per cent; cardia, 18 per cent; "extensive," 26 per cent. In a similar study by Feldman and Morrison, the distribution of 91 cases was as follows: pylorus, 43 per cent; fundus, 27 per cent; cardia, 19 per cent; and "whole stomach," 11 per cent. With fewer "extensive" cases in the latter study as compared with the former, a marked increase is noted in pyloric cases; a modest increase in fundus cases; and a slight increase in cardia cases. Using these two studies to hazard a prediction of the distribution of stomach cancers by location if none were advanced to the "extensive" category, it would appear that as high as 50 per cent might involve the pylorus; 30 per cent the fundus; and 20 per cent the cardia.

From the medical literature one finds that achlorhydria is mentioned frequently as a sign of gastric cancer and is invariably present in patients with pernicious anemia. It has also been shown that achlorhydria often precedes gastric cancer, sometimes by many years. Several investigators have noted an increased incidence of gastric cancer among patients with a diagnosis of pernicious anemia. Thus, Zamcheck, Grable, Ley and Norman found, in a follow-up study of 1222 patients with pernicious anemia diagnosed between 1915 and 1951, that the incidence of subsequent gastric cancer was 10 per cent or about six times the rate expected in the general population. Likewise, Berkson, Comfort and Butt reported that among 1058 patients found to have achlorhydria in the years 1935 to 1938 the subsequent incidence of gastric cancer was six times that of the general population. Some 225 of these same patients had a diagnosis of pernicious anemia and were studied as a special group. Although none of these patients had gastric cancer at the time the diagnosis of pernicious anemia was made, they subsequently developed gastric cancer at a rate which was eight times that expected for the general population.

The figures presented above are derived from clinical studies covering extended periods of time and should be considered as something less than refined indications of the probabilities involved. They are subject to the biases which are often inherent in "selected" case studies, particularly among patients admitted to hospitals. Any individual case may prove to be the exception to the rule or may show up in some extreme position on the probability scale.

A search of the literature reveals no information on the "odds" of developing cancer in the portion of the stomach remaining after partial resection for gastric ulcers. However, Ravdin and Horn report "up to 10 per cent of gastric cancer at the site of the benign ulcer." The 1951 Impairment Study by the American Society of Actuaries indicates that the mortality from gastric cancer among insured persons with a past history of gastric ulcers, whether or not there was surgical inter-

vention, is about twice that found among insurees without such history. In determining the rates for substandard risks the insurance companies rely on their own mortality experiences among persons with physical impairments. On the more common impairments data are readily available for the computation of substandard rates. In the case of mutiple impairments, particularly the rare combinations, the necessary data for establishing rates are more difficult to obtain and I am informed by the Society of Actuaries' Committee on Mortality that these rates are determined on an individual basis, subject to the best judgment of the examining physician. In view of the fact that the insurance companies are required to publish their premium rate schedules, both standard and substandard, it is not always possible, in the best judgment of the examining physician, to recommend for a given applicant a suitable rate from among those published. In this sense, certain individual cases may be considered uninsurable. However, the insurance companies are constantly studying the enormous problems of shifting morbidity and mortality and whenever possible are extending the limits of individual insurability. Hence, a vigilant and hopeful outlook on the part of the inquiring physician may yet pay off in terms of an underwriter who will provide for his insurance needs.

At the risk of facing all the hazards inherent in passing from the scientific to the philosophical, the writer would like to extend a word of encouragement to the physician because he, the writer, is also "uninsurable." At least he has never felt it advisable to pay the extra premium (quoted some years ago at a figure equivalent to the standard premium of a person twice his age at that time) just for the sake of having life insurance. The solution of the problem in his case required three things: (1) accepting the facts; (2) making a decision; and (3) living with that decision—peaceably. Strangely enough, the "diagnosis" of uninsurability has not proven to be entirely "fatal" over nearly half a century! As a matter of fact, it has had its compensations—largely in terms of the development of a philosophy of life which includes: (1) a deep sense of appreciation of being alive (in spite of physical limitations and nagging symptoms); and (2) a sound conviction that security can rest on something more substantial than a life insurance policy. This philosophy is probably better expressed by Bauer in the preface of his book YOUR HEALTH TODAY: "The indomitable spirit with a broken spine is a better man than the Adonis with a wishbone where his backbone ought to be." From such a philosophy can spring an inner strength that is more valuable than the highest-priced life insurance policy ever written.

The doctor-patient's consultant internist: Dr. Joseph B. Kirsner

Regarding the advantages and disadvantages of annual or more frequent roentgen examinations of the stomach, I would agree as to the potential hazards of extensive radiation. I also would doubt the value of such frequent x-ray examinations of the stomach in dealing with this problem. Careful clinical observation and repetition of appropriate laboratory tests including blood counts and examination of the stools for blood, together with other procedures mentioned later, should provide as adequate diagnostic supervision as is currently possible. I had originally recommended an upper gastrointestinal series every two years as a rather arbitrary program; certainly the intervals could be lengthened if the patient's general health and laboratory studies remain satisfactory.

The comments with regard to the increased incidence of gastric neoplasm in patients with pernicious anemia and in patients with true anacidity and extensive atrophy of the stomach require no further elaboration; I would agree. However, I find it difficult to accept completely the diagnosis of pernicious anemia in this case, at least on the basis of present evidence. Of course, a small amount of vitamin B_{12} can eliminate any hematological evidence of pernicious anemia; on this basis, it may not be possible to include or exclude such a diagnosis at this time. How-

ever, inasmuch as this is a critical problem for the patient, it might be worthwhile to consider additional tests. These procedures might include an adequate gastric analysis utilizing a potent stimulant of gastric secretion—histamine, histolog or possibly reserpine. I think it has been demonstrated clearly that many of the tests purported to demonstrate gastric anacidity are not completely adequate; and that when adequate stimulation is employed and pH determinations are made of the subsequent gastric specimens the presence of HCl can be demonstrated, not infrequently in substantial quantities. Additional absorption studies with B_{12} cobalt-60 might be worthwhile; perhaps a series of such tests: (a) without intrinsic factor, (b) with intrinsic factor and perhaps, (c) after the administration of a broad spectrum antibiotic for several weeks, should the B_{12} test with intrinsic factor continue to demonstrate reduced absorption. This last point is suggested on the basis of our experience with the blind loop syndrome in which the poor absorption of B_{12} tends to be corrected when presumably an unidentified bacteriological disturbance within the loop is modified by antibacterial therapy. Still another procedure that might have bearing on this question would be gastroscopy with gastric biopsy. There are adequate instruments for this purpose. However, the value of the technique is perhaps in direct proportion to the experience of the examiner and to the diffuseness of the process within the stomach. I should think an experienced and skilled examination of this type might provide us with useful information.

To review my recommendations: I would suggest an upper gastrointestinal x-ray series at intervals of two years, but possibly at longer intervals if the patient is well. If cytologic examination at six-month intervals indicates suspicious or questionable findings, gastroscopic examination should be made. We have found expert cytologic studies to be extremely valuable in the recognition of gastric malignant neoplasm, and we now place considerable emphasis on this technique in our own laboratory. An interesting observation, at least in some patients with pernicious anemia, is the continued presence of so-called PA cells, despite therapy to the point of complete restoration of the peripheral blood count and the bone marrow. The earlier observation in our laboratory that this patient's gastric cytology was entirely normal might, on this basis, be taken as evidence against the presence of a true pernicious anemia. The gastric cytologic test might be repeated every six months; perhaps expert gastroscopy could be made each year. Intramuscular injection of 100 micrograms B_{12} should be given monthly indefinitely. The patient's continued good health and the maintenance of his blood count would suggest that perhaps he is not in as vulnerable or critical state as might have been feared.

[Further suggestions for this physician-patient's medical and insurance management would be appreciated. For additional discussion of this interesting case see *J. A. M. A.* 169:779-780, Feb. 14, 1959. —Ed.].

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new developments in cancer

Thyroid and Breast Cancer . . .

More than four years ago, Dr. A. A. Loeser of London reported greatly increased survival rates in metastatic breast cancer cases who had been given thyroid hormone regularly following radical mastectomy. A clear majority of patients with lymph node involvement were alive and well, at that time, four years or so following surgery. The report stimulated comment but virtually no effort was made to confirm or invalidate his results. More recent publications (the March, 1958, *Journal of the International College of Surgeons* and, later, letters to *Lancet* and the *British Medical Journal*) have brought results in England. Dr. Loeser reports that thyroid now is given routinely following radical mastectomy in several hospitals—St. Mary's, St. Bartholomew's and Rochester. Investigators at the Cancer Hospital and Middlesex Hospital also have begun to test the effects of the hormone postoperatively.

Microscopic Control . . .

For more than 15 years, Dr. Frederic E. Mohs, of the University of Wisconsin Medical School, has used his microscope to make certain that, before discharging a patient, he had removed all the skin cancer. The care has paid off. His five-year cure rates for skin cancer are: basal cell, 98.2 per cent of 1071 cases; squamous cell, 84.8 per cent of 483 cases; melanoma, 41.2 per cent of 35 cases. One third of more than 1500 cases were recurrent lesions, many of them hazardous or impossible to treat by conventional surgery or radiation. Perhaps a primary virtue of microscopy-controlled treatment is its conservatism—the sparing of normal tissue makes possible excellent cosmetic results. The operation itself is simple and brief. Uninvolved cases take less time and trouble than the average tooth extraction. Under local anesthetic, the visible tumor is lifted out surgically, immediately sectioned and examined microscopically by a pathologist. The tumor bed is covered with an adhesive, tissue-destroying fixative, and the patient is told to return the next day. On the second visit, the dead, fixed crust is lifted out and its sections examined microscopically. If cancer cells are found in the crust, that particular area of the tumor bed is treated with cytolytic chemicals, the new tumor bed is covered with the same fixative and the procedure repeated. One or two treatments usually are required for early localized cancers. Sometimes, more treatments are needed.

thoracotomy or laparotomy. Over the entire spectrum of brain tumors and under ideal conditions, about one-half the patients can be cured by surgery. They pointed out that CNS tumors are among the three most frequently encountered in practice -- most commonly affecting females under 20 and males under 40. Symptoms from cerebral metastases often are the first signs of cancer of the lung, mediastinum and breast, among other sites.

Anderson (U. of Miami) said that metaplasia and atypical hyperplasia, sometimes precursors of cancer, may be mistaken for cancer under both radiologic and cytologic examination. This is true when the growths are in the bronchial epithelium or in the lining of the bronchioles. The source of these confusing nodules lies in scar tissue or inflammation due to atmospheric contaminants, tobacco smoke, air pollutants and infection.

Garland (Stanford) said that benign single nodules of the lung can be differentiated from malignant nodules with 95 per cent accuracy by observing a simple set of rules. The rules, in brief, are: (1) Compare new x-ray pictures with old ones; (2) consider the age, sex and habits of the patient; (3) take symptoms into account and (4) evaluate the properties of the x-ray shadow carefully. Malignancy would be suspected in a male smoker over 55 with a nodule that has fuzzy edges and contains no calcium. Good signs include female sex, under 45, shadows with sharp edges, recent surgery in the lung region or hematoma from needle puncture, or infection (virus pneumonia, aftermath of tooth extraction, exposure to coccidiosis, histoplasmosis or tuberculosis).

Gellhorn (Columbia) reported that preliminary results indicate that atabrine may be helpful in controlling fluid accumulation.

The concept of DNA being a double-stranded, spiralling train of linked nucleotides has been shaken severely by a finding by Sinsheimer (Cal. Tech.) of a single-stranded DNA. The single strand molecule of DNA was found in a bacteriophage labeled ϕX174, which appears to be unique among viruses. The virus itself is a dwarf -- in its protein coat; its single DNA molecule has a weight of about 36,000, which puts it in the class of polio and plant RNA viruses in this respect (virus DNAs range, roughly, from 13 to 40 times that molecular weight); and, like RNA but unlike other DNAs, formaldehyde inactivates it. Scores of concepts, postu-

lates, theories and even calculations, involving reproduction, ageing, infection and other basic biochemical aspects of life, now must be reconsidered in the light of the Cal.-Tech. findings.

Sandberg and others at Roswell Park have observed, with complete consistency so far, the appearance of a non-dialyzable, heat-stable polypeptide in the urine of a variety of leukemic patients. The material prevents the precipitation of nucleic acids by trichloroacetic acid. It has been isolated as a crude extract from leukemic urine -- but not from nonleukemic urine.

Various . . .

Nemeth (Budapest): Rats given (600 r) x rays before transplantation of Guerin's cancer had increased metastases; very heavy doses (6 x 300 r) after transplantation inhibited metastases and prolonged survival. Mannite mustard in small doses (3 x 10 mg.) after transplantation inhibited metastases, prolonged survival and sometimes gave complete healing.

Burdette (Salt Lake City): Ecdysone, the fly metamorphosis hormone, caused regression of a few transplanted mouse tumors.

Rygard (Copenhagen): Some leukemogenic treatments have been shown to lower resistance to infections. Phagocytosis seems the most important defense against infections. Phagocytotic clearance of radiogold from mouse blood is depressed within the first month following use of x ray, x ray plus androgen and painting with 9:10-dimethylbenzanthracene, with and without androgen. Leukemic mice and even young pre-leukemic mice show depressed clearance.

Friend (New York): Mice pretreated with mouse or rabbit antiserum against a filterable leukemic agent were protected to a significant degree. Three shots of formalinized vaccine protected over 80 per cent of the animals.

Stewart, Eddy and Stanton (Bethesda): An agent which causes a variety of cancers in hamsters proved highly antigenic -- rabbit antisera completely protected hamsters against it.

Holland and Cuddihy (Buffalo): The supernatant of Ehrlich ascites fluid, intraperitoneally inhibits the growth of several experimental tumors. Nonmalignant ascites fluid doesn't.

COMING MEDICAL MEETINGS

Date 1959	Meeting	City
Apr. 18-21	Texas Medical Association	San Antonio
Apr. 19	American Society of Internal Medicine	Chicago
Apr. 20-23	American Urological Association	Atlantic City
Apr. 20-24	American College of Physicians	Chicago
Apr. 21-23	American Association for Thoracic Surgery	Los Angeles
Apr. 23-25	American Association of Pathologists and Bacteriologists	Boston
Apr. 23-25	Hawaii Medical Association	Hilo, T. H.
Apr. 26-29	Industrial Medical Association	Chicago
Apr. 27-29	Aero Medical Association	Los Angeles
Apr. 30-May 3	Student American Medical Association	Chicago
May 2-3	American Psychosomatic Society	Atlantic City
May 2-9	Conference on International Union for Health Education of the Public	Dusseldorf, Germany
May 3	American Federation for Clinical Research	Atlantic City
May 3-4	American Society for Clinical Investigation	Atlantic City
May 5-6	Association of American Physicians	Atlantic City
May 6-8	American Pediatric Society	Buck Hill Falls, Pa.
May 8-9	Society for Pediatric Research	Buck Hill Falls, Pa.
May 9-15	Medical Society of the State of New York	Buffalo, N. Y.
May 10-14	American Society of Maxillofacial Surgeons	Chicago
May 10-15	Society of American Bacteriologists	St. Louis
May 19-21	Massachusetts Medical Society	Boston
May 21-23	American Association for the History of Medicine	Cleveland
May 24-29	National Conference on Social Welfare	San Francisco
May 25-27	American Gynecological Society	Hot Springs, Va.
May 25-27	American Trudeau Society	Chicago
May 26-29	American College of Cardiology	Philadelphia
May 28-30	American Ophthalmological Society	Hot Springs, Va.
June 1-4	American Dermatological Association	Atlantic City
June 3-7	American College of Chest Physicians	Atlantic City
June 4-5	American Geriatrics Society	Atlantic City
June 4-6	The Endocrine Society	Atlantic City
June 4-7	American Medical Women's Association	Atlantic City
June 4-7	American Therapeutic Society	Atlantic City